STITT'S
DIAGNOSIS, PREVENTION AND TREATMENT OF TROPICAL DISEASES

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DISEASES CAUSED BY FILTRABLE VIRUSES, RICKETTSIAE, OR ALLIED ORGANISMS

Chapter XXIII

YELLOW FEVER

Progress in the study of yellow fever in recent years has been due particularly to the fact that a number of efficient workers have been willing to devote their energies for a period of years especially to the study of this disease. The danger of the spread of the infection, especially through infected mosquitoes, has made it imperative that experimental work be carried out in special laboratories and with proper precautions.

Dr. A. W. Sellards has been conducting his studies upon yellow fever at Harvard University and abroad since 1927 and has become an outstanding authority upon the subject. Therefore it is especially fortunate that he has been willing to prepare the present chapter. (R.P.S.)

Introduction.—Yellow fever is one of the more complicated of the infections of man but many of the essential features of the disease are well understood, more especially the typical pathology, the characteristics of the causative virus, its behavior in man and in the mosquito vector, many of the details of the môde of transmission by *Aëdes aegypti*, and the interesting effects which the virus produces in animals. Beginning in 1881 and continuing for nearly 20 years, Finlay conducted observations and many human experiments which led him to conclude that the aegypti mosquito transmits yellow fever. In 1898 Carter worked out the approximate limits of the "extrinsic incubation" period but with no thought of insect transmission. Another period opened in 1900 when Reed, Carroll, Lazear and Agramonte by infection of volunteers demonstrated for the first time the essential features necessary for successful transmission by the mosquito, *A. aegypti*. In their investigations concerning etiology, Reed and his associates supplied convincing evidence that yellow fever is a virus disease. In 1928, many laboratories undertook extensive experimental investigation when the susceptibility of the rhesus monkey was reported. In 1932, a procedure for the immunization of man was introduced in order to utilize mass vaccination as a method for the control of yellow fever. In referring to the literature in this chapter it is not

feasible to include the many valuable articles of a confirmatory nature but a careful effort has been made to select the original observations. One may await with interest the developments concerning the existence of yellow fever in the wild life of the forests. Clinically, the treatment of yellow fever remains in an unsatisfactory state in that no specific therapy is available, once the infection has become established.

Synonyms of importance:—None.

Designation in other languages: Fièvre jaune (Virus Amaril), Febbre Gialla, Fiebre Amarillo, Gelb fieber.

Definition.—Yellow fever is an acute infectious jaundice caused by a virus which, in the typical epidemics of cities, is transmitted from man to man by the mosquito, *A. aegypti*. Fatal cases show an extensive necrosis of the liver which tends to be mid-zonal in its distribution. Recovery is accompanied by the development of a lasting immunity.

History and Geographical Distribution

Historical.—Carter (1931) attributes the first definite description of yellow fever to Lopez de Cogolludo in Yucatan in 1648, whereas one finds the first clear recognition of the disease in Africa in Schotte's account of the outbreak among the British troops in Senegal in 1778. However, there is much evidence which indicates that Africa may have been the original home of yellow fever. Presumably both the virus and the insect vector (*A. aegypti*) were brought to the New World during the days of the slave trade. On entomological grounds, the aegypti mosquito appears to be an importation into the New World since there are many species of mosquitoes more or less closely related to *A. aegypti* in Africa but there is no other member of the subgenus *Stegomyia* which is native to the Americas. Carter (1931), a lifelong student of yellow fever, concludes that the biological evidence, though not conclusive, is altogether in favor of an African origin and that the available historical evidence is entirely consistent with this view. In former years, serious outbreaks of yellow fever have occurred in southern Europe and in the Americas. The United States has experienced numerous severe epidemics, notably the one occurring in Philadelphia in 1793, another centering in Memphis in 1878, and that of 1905 in New Orleans, but this is usually considered as the last one that this country need expect. The period is almost forgotten when with the coming of the summer months, outbreaks might be expected in our southern states. The opening of the Panama Canal caused, for a short period, some serious apprehension that the increased traffic across the Pacific Ocean might lead to the introduction of yellow fever in the Orient. The geographical distribution of yellow fever does not correspond with the distribution of its vector *A. aegypti*. The Orient with its susceptible population and its abundance of suitable mosquitoes has at all times remained free of yellow fever and for this good fortune no explanation is forthcoming. Dengue fever is carried by *A. aegypti* in essentially the same manner as yellow fever and dengue is prevalent not only in Europe and America but also throughout the Orient.

The data based on the clinical diagnosis of yellow fever indicated that the endemic foci were limited to a few restricted areas in West Africa and in South America. The application of a practical laboratory method of diagnosis revealed two vast endemic zones that had escaped detection. Theiler (1930), working in the Department of Tropical Medicine at Harvard, introduced protection tests in mice. Convalescent serum, even many years after an attack of yellow fever, neutralizes the virus specifically, and affords protection to mice against an otherwise fatal infection. This immunity test was promptly adopted by various workers in England, Belgium, France and more especially, on a very extensive scale, by Sawyer and his associates in the Rockefeller Foundation. In Africa, the endemic zone was found to extend eastward more

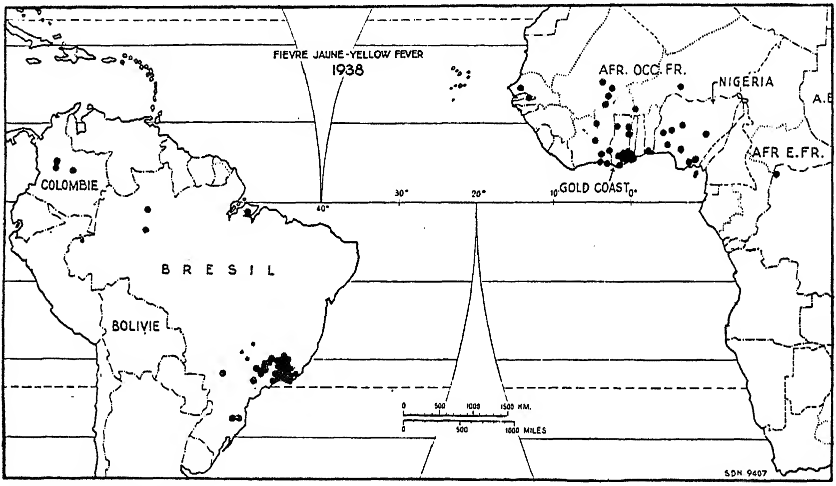

FIG. 198.—Distribution of Yellow Fever, 1938. (Epidemiological Intelligence Service of the League of Nations.)

than 3,000 miles to the upper Nile with the Sahara Desert forming a barrier to the northward (Sawyer et al, 1937). The second zone was discovered in Brazil along the Amazon basin (Soper, 1937) and includes important areas of some of the neighboring countries, notably Colombia and Venezuela. In some unpublished observations, Strong, in 1937, demonstrated the occurrence of yellow fever in Perú under sylvatic conditions. Some of the regions which have been recognized by immunity tests are frequently spoken of as "silent foci" but this interpretation should be regarded with reservation. With increasing opportunities for clinical observation, typical cases of yellow fever have been observed in some of these so-called "silent areas" and fatal cases undiagnosed during their illness have been recognized at autopsy.

The potential menace of these vast endemic zones contrasts rather sharply with the recognized cases as shown in the accompanying map from the League of Nations.

The Specific Etiologic Agent and Its Properties

The fact that yellow fever is caused by a virus which readily passes bacteria-proof earthenware filters was demonstrated convincingly in 1902 by Reed, Carroll, Agramonte and Lazear of the Army Commission in Cuba (Senate document, 1911) and by Marchoux, Salimbeni and Simond (1903) of the French Commission in Brazil. No new evidence concerning filtrability was added until Findlay and Broom (1933), using Elford's technique of ultrafiltration, assigned a probable size of 17 to 28$\mu\mu$ to the virus particles. The virus is sensitive to physical and chemical agents. It is readily killed or at least rendered non-infectious by drying by heat and chemical disinfectants. A temperature of 55° for 5 or 10 minutes is often sufficient to kill the virus (Reed et al; Marchoux et al). Suspensions of virus in saline may become non-infectious within 2 or 3 hours at room temperature, but a little protein (10% of serum) will prevent this rapid deterioration (Bauer and Mahaffy, 1930). The virus is readily preserved in the cold and infective tissues remain virulent for many months if stored at a temperature a little below 0°C.

The antigenic properties of the virus are evident inasmuch as immunity and a highly protective serum develops as the result either of an inapparent infection or a serious illness. Much effort has been spent by several investigators on immunity reactions *in vitro* such as tests for precipitins and complement fixation. The results, though of theoretical interest, have not achieved the status of a practical procedure.

In the etiologic era of bacteriology, various microörganisms were described as the specific cause of yellow fever. Chief among these was *Leptospira icteroides* obtained in 1919 by Noguchi (1925) from cases in Guayaquil which he considered to be yellow fever. For nearly a decade this leptospira was accepted as a distinct species and regarded as the specific cause of yellow fever. This conclusion appeared to be adequately supported by the strikingly favorable results reported in serum treatment and in vaccination. More than 20,000 individuals were vaccinated with killed cultures of leptospira and the statistical data indicated specific protection against yellow fever, but these vaccinations may, in fact, have afforded protection against Weil's disease. The author (Sellards, 1927) concluded that yellow fever is not caused by any species of leptospira. The mosquito *Aëdes aegypti*, does not transmit leptospira to man or to susceptible animals by its bite (Gay and Sellards, 1927). *L. icteroides* is identical with *L. icterohaemorrhagiae* which in turn is a synonym of *L. interrogans*, the name which properly applies to the specific cause of Weil's type of infectious jaundice (Sellards, 1940).

Pathology and Pathogenesis

The yellow color of the sclerae and the skin usually becomes quite distinct with the blanching of the skin after death. Haemorrhage into the stomach or intestines with extreme darkening of the blood affords a striking picture but this may also occur in leptospiral jaundice. The

liver, about normal in size, may be red from extravasation of blood or very yellow because of fatty degeneration, but the question of necrosis cannot be determined with any degree of satisfaction by gross examination.

The essential lesion is a necrosis of the liver which in its earlier stages is frequently, though not always, midzonal in its distribution, but this characteristic often becomes obscured by widespread involvement of the lobules comparable in some measure to acute yellow atrophy. The destruction of liver tissue affords an adequate explanation for the immediate cause of death. The pathology in rhesus monkeys (*Macaca mulatta*) is essentially the same as in man. Amorphous acidophilic degenerations were reported by Torres (1928) in the nuclei of the liver parenchyma

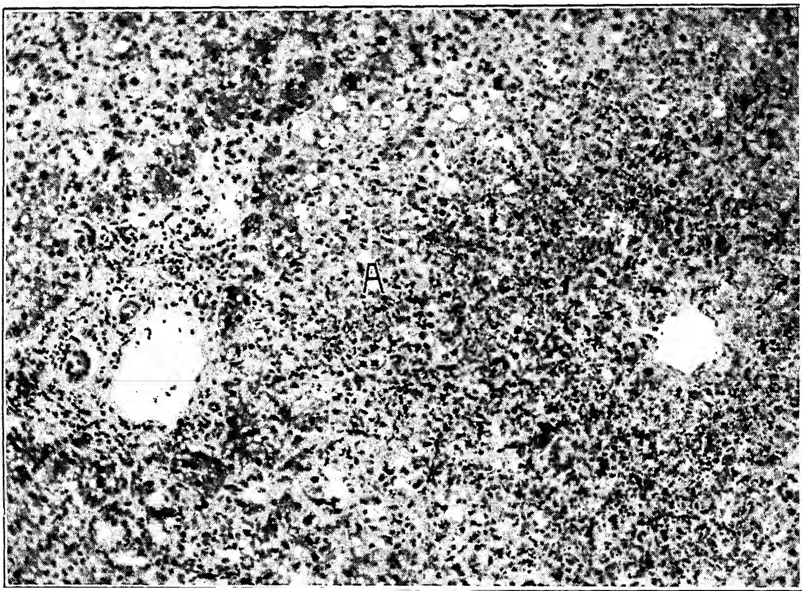

FIG. 199.—Section of liver in yellow fever showing (A) necrosis of the parenchyma. × 715. (Army Medical Museum photo No. 46958.)

and these occur abundantly in the monkey and less frequently in man. These nuclear changes have also been described and illustrated by Cowdry and Kitchen (1930), and though not pathognomonic they are of supplementary value in diagnosis. At one period, the identity of yellow fever in Africa and in America was brought into question but Tyzzer (1928) in the study of autopsy material from cases occurring in Senegal and Ecuador noted complete agreement in the pathological processes in both series of cases. Klotz and Belt (1930) reached a similar conclusion and they described some of the less striking changes in other organs such as granular and fatty degeneration of the kidneys, degeneration and hyperplasia in the spleen, and petechial haemorrhages in the lungs. The degenerative changes in the musculature of the heart include the conducting system (Lloyd, 1931).

Although the virus of yellow fever is highly neurotropic, patients do not develop frank cerebral symptoms nor any extensive lesions of the central nervous system. The blood brain barrier is well developed in the adult but it is much less effective in children. If the central nervous system were invaded by the virus, the rapid necrosis of the liver might mask the more slowly developing lesions of the brain, or conceivably a rapidly developing immunity might check the infection. These conceptions do not seem quite adequate and the marked neurotropism of the virus invites attention to the possibility of re-investigating the symptoms and lesions of yellow fever especially in infants. The neurotropic virus of yellow fever when inoculated intracerebrally in the monkey leads to an acute disseminated encephalomyelitis with necrosis of the sensory and motor ganglion cells and the development of inclusion bodies (Goodpasture, 1932).

The virus presumably is obligately intracellular in its habitat but the site of the initial lesion and the tissues in which multiplication takes place is open to conjecture. Infective blood of monkeys may contain virus in dilutions as high as 1 to 50,000,000 or even 100,000,000 and in monkeys the virus penetrates cell-free and almost protein-free fluid such as the aqueous humor of the eye (Sellards, 1930).

Some of the features in the pathogenesis of yellow fever have an interesting bearing in regard to the symptomatology and treatment of the disease. Rapid and extensive necrosis of the liver from any cause leads to abnormalities in the composition of the urine. During the epidemics of yellow fever at Dahomey and Dakar, Pichat (1929) examined more than 2,000 specimens of urine. During the first two days of illness the amount is usually abundant but the chlorides diminish rapidly. Toward the end of the second day albumin appears in traces and increases to as much as 10 grams daily. In severe cases, peptones are excreted in the urine about the fourth day of illness and increase until death. In Dakar on ward rounds we frequently observed patients whose clinical progress appeared to be reasonably satisfactory but on visiting Pichat in his laboratory he could quite accurately predict a serious prognosis in those showing a marked peptonuria. The appearance of bile pigments in the urine was regarded as a favorable indication. The composition of the urine returns to normal toward the end of the first month of convalescence. Pichat concluded that yellow fever can be distinguished from other infections by the composition of the urine.

The rapid destruction of hepatic parenchyma leads to serious disturbances of the carbohydrate metabolism. The exact chemical studies in experimental yellow fever by Wakeman and Morrell (1931) demonstrated a hypoglycaemia with regularity, a depletion in the glycogen of the liver, and an impairment of its glycogenic function. The hepatic lesions might also lead to an increase in the guanidine-like substances in the blood and a slight increase has been reported in monkeys (Findlay and Hindle, 1930) and in man (Berry and Kitchen, 1931). The changes in the values for blood sugar and guanidine would be consistent with the muscular twitchings and the gastro-intestinal lesions occurring in patients.

Mode of Transmission

The early literature contains vague suggestions concerning a possible relationship between insects, climate and the spread of yellow fever. In the epidemic of 1797 in Philadelphia, Rush (1798) noted that "on the nights of the 12th and 13th of the month (October), there was a froſt accompanied with ice, which appeared to give a ſudden and complete check to the diſeaſe." In 1881 Finlay commenced a series of investigations on the transmission of yellow fever by a species of *Stegomyia* mosquito, now usually designated as *Aëdes aegypti;* by 1900 he had conducted more than 100 experiments on volunteers, of whom a small proportion developed yellow fever (Selected Papers, 1912). Finlay concluded that *A. aegypti* is the vector of yellow fever and advocated measures against this mosquito as a practical means of control; he noted also that even under apparently favorable conditions fomites appeared to be innocuous. These observations were published in the scientific periodicals of the New World, of Europe and Great Britain, but medical authorities, in their efforts at control measures, continued to concentrate their attention on fomites and on disinfection. Finlay's experiments were made under circumstances which did not exclude natural infection and, moreover, his conception of the mechanism of transmission by the mosquito was incomplete. In the endemic area of Cuba there had been little or no opportunity to observe and study the unexpected delay that occurs between primary and secondary cases. In a region free of yellow fever various observers had noted that the introduction of an early case of the disease was followed by a period of about 2 to 3 weeks of apparent safety and then under favorable conditions secondary cases made their appearance in considerable numbers. This curious phenomenon remained unexplained since it was quite unlike anything known at that time, concerning the ordinary infectious diseases. Corré aptly designated this delay as the "extrinsic incubation period," a phrase which subsequent observers have frequently attributed to Carter. The limits of this extrinsic period were worked out with considerable exactness by Carter (1900) at Orwood, Mississippi, and his description of this locality illustrates the exceptionally favorable circumstances which arose for this classical study in epidemiology.

> Orwood is not a town, or even a hamlet—it is a "neighborhood"—an agricultural community about 12 miles from the railroad at Taylor, consisting almost exclusively of white people, living on their farms, seldom closer than a mile apart, working their own lands with little hiring, having little intercourse with the outside world, practically all non-immune to yellow fever; intelligent, law abiding, and well disposed; people who were at once intelligent enough to know and honest enough to tell the truth and to coöperate in good faith with the efforts made to trace the infection of each case and by stopping visiting to limit the spread of the infection already introduced.

One case of yellow fever of only moderate severity was introduced at Gray Mansion, one of the homes at Orwood. A week passed uneventfully, the members of the household remained well, a second week passed and the incident was almost forgotten. After an interval of 18 days

secondary cases began to appear in rapid succession. Of 46 people exposed at Gray Mansion, 45 became infected. The one who escaped may have been an immune.

With no thought of an insect vector, the extrinsic incubation period was used, in a limited way, as the basis of a rational plan for the protection of persons living in communities where yellow fever had been recently introduced. Voluntary isolation camps were formed at a convenient distance from any active focus, such as the one in 1899 near Jackson, Mississippi. To be eligible for admission to this camp, applicants were required to come within a few days of the appearance of the first case of yellow fever in their community. Carter (1900) comments that no infections were expected in this camp and none developed.

At this point, the investigations in Cuba were continued by a Commission of the United States Army, namely, Reed, Carroll, Agramonte and Lazear, and it remained for them to bring exact proof of the rôle of the mosquito in yellow fever (Senate document, 1911). All of the experiments were conducted on volunteers obtained chiefly from the United States Army and the Spanish civil population. Finlay kindly supplied the Commission with a strain of *Stegomyia* mosquitoes, with information about their habits and with the confident assurance that no other mosquito need be considered. The volunteers were isolated near Havana at an experimental station which was subsequently known as Camp Lazear after the death of Dr. Lazear from yellow fever. The first 9 men remained well after being bitten by mosquitoes which had fed on yellow fever patients. Dr. Finlay expressed full confidence in his conclusions and that some change in the experimental conditions would explain these failures. Eight of these 9 men had been bitten by only one mosquito, with the incubation time in the mosquito varying from 2 to 10 days. In the next experiment, Dr. Carroll who had been isolated except for two visits to the endemic zone, was bitten on different occasions by several mosquitoes, and one of these had fed on an early case of yellow fever 12 days previously. A severe infection developed ending in recovery and with this encouragement, the work was continued with volunteers kept in rigid isolation.

Briefly, the Commission demonstrated that (1) the blood is infective for a mosquito only during the first 3 days of a patient's illness; (2) a period of approximately 12 days must elapse before the mosquito can transmit the infection; (3) the mosquito remains infective for the duration of her life. These conclusions have stood the test of time and the only change has been the addition of details of information. Thus the exact incubation time in the mosquito is dependent on the weather, and may vary from 4 or 5 days at 37°C. to as much as 3 weeks at 20°C., though the period of 12 days may be accepted as a reasonable estimate for ordinary conditions. Thus the extrinsic incubation period of Corré comprises the usual incubation time of nearly 2 weeks in the mosquito plus the incubation period of a few days in man. The unique situation arises that the incubation time in the mosquito was estimated at Orwood with

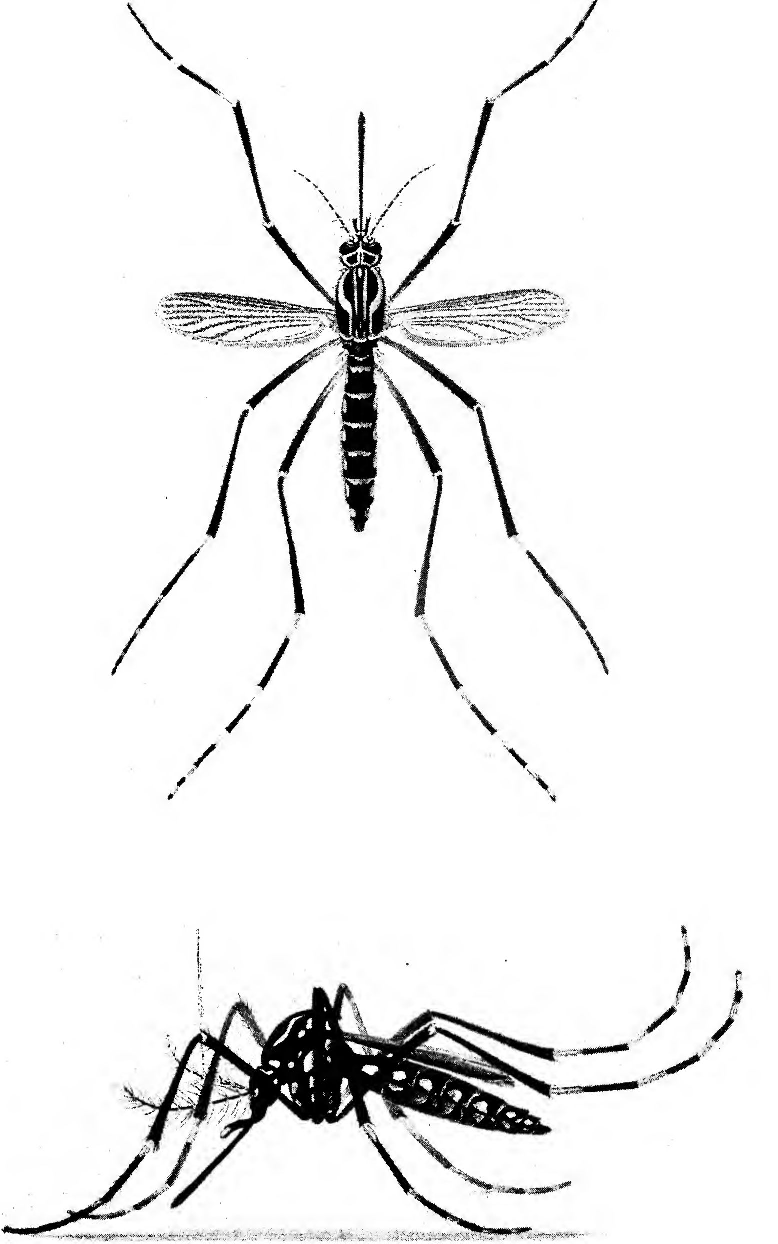

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FIG. 200.—*Aëdes aegypti.* Female. Dorsal view and usual posture when resting. (From: Goeldi, "Os Mosquitos no Pará," Pará, 1905.)

considerable exactness without recognizing that the infection was transmitted by insects. The brilliant results of anti-mosquito campaigns in Cuba and in the Americas led eventually to a plan for world-wide eradication of yellow fever, and this difficult undertaking achieved a remarkable measure of success under the auspices of the Rockefeller Foundation with results of permanent value in cities of North and South America. The available evidence from experimental and from epidemiological sources indicated at this period that the virus of yellow fever in nature is limited quite strictly to man and the one species of mosquito, *Aëdes aegypti*. However, in Great Britain, Fowler and his associates (1916) had emphasized the necessity of looking for vectors other than *A. aegypti* and for infections occurring naturally in lower animals, a viewpoint which has gained ground in recent years.

Many species of mosquitoes transmit yellow fever by their bites from monkey to monkey under experimental conditions. Within 4 years after the recognition of the susceptibility of the rhesus monkey, Hindle (1933), in reviewing the literature, listed 13 species of mosquitoes in West Africa as transmitting the virus by their bites in a more or less effective manner. Nine of these species belonged to the genus *Aëdes*, the other genera being *Eretmopodites*, *Culex*, *Mansonia* and *Anopheles*. Other species and even other genera have been added to this list, notably three species of *Aëdes* and one of *Haemogogus* in South America, *A. geniculatus* in France and *A. albopictus* in the East Indies (Sawyer, 1939). The neoartic mosquito *A. triseriatus* occurring entirely outside the endemic zones of yellow fever, transmitted the infection experimentally but not in the efficient manner of *A. aegypti* (Bennett et al, 1939). In some instances, doubtful or conflicting results have been reported by investigators using apparently the same technique. Successful transmission by various kinds of mosquitoes under artificial conditions of the laboratory does not in itself imply that these species are of epidemiological importance. Indeed *A. aegypti* remains as the vector responsible for the extensive urban outbreaks of yellow fever. The search for other vectors has proved to be a time-consuming undertaking. Thousands of mosquitoes caught in the forests of Brazil were allowed to bite rhesus monkeys and the virus of yellow fever was demonstrated in two genera, *Aëdes leucocelaneus* and *Haemagogus capricornii* (Shannon et al, 1938). An even more difficult task has been encountered in the search for an animal in nature which might serve either as a susceptible host or as a reservoir for the virus. The hedgehog has been considered because of its susceptibility to yellow fever (Findlay and Clarke, 1934). The blood of monkeys from endemic zones of yellow fever occasionally affords protection to mice (Findlay et al, 1936). Similar results have been recorded by Soper (1936) and others.

Epidemiology

The môde of transmission of yellow fever affords a reasonably clear understanding of its epidemiology. In the extensive epidemics of cities,

the infection is spread rapidly by the vector *A. aegypti.* In some of the former endemic foci such as Cuba, the virus was maintained continuously in man and the aegypti mosquito with no indication of any other vectors or of infections in lower animals. This môde of transmission involves a delicate balance of factors which, at times, seems barely sufficient for maintaining the existence of the virus. Thus it is necessary that susceptible individuals must be available, the blood of the patient is infective only for a few days, and the life of the mosquito is short, perhaps, in nature, about one month. In some of the islands of the West Indies yellow fever disappeared spontaneously.

Frequently, severe and even fatal cases of yellow fever, if they occur in sporadic form, are not diagnosed correctly, the disease remaining unrecognized until it reaches epidemic proportions. In communities opposed to autopsies, an instrument described as the viscerotome has been introduced for puncturing the abdomen of the cadaver and removing a portion of liver for histological examination. This procedure is hardly less objectionable than an autopsy in regions were any postmorten examination is regarded in sincerity as a violation of the dead. In Brazil the viscerotome service has required the support of legalization by executive decree. The technical organization of this service has been described in detail by Rickard (1937) and the difficulties have been emphasized by Rickard and also by Soper (1937). Thus it is customary to pay the layman performing viscerotomy in proportion to the number of samples submitted. At times multiple specimens from one person dead of yellow fever have been sent under several fictitious names and occasionally liver tissue of lower animals including avian species have been received by the pathologist. The outstanding advantages of the service to the epidemiologist are evident from the experience of Soper, Rickard and Crawford (1934). The examination of more than 28,000 specimens of liver collected chiefly in Brazil established the diagnosis of yellow fever in 54 cases, and 43 of these came from localities in which the presence of yellow fever had not been recognized.

The experimental evidence concerning the existence of sylvatic yellow fever is meager, but epidemiological observations in South America indicate that endemic zones of infection exist in forest regions where sporadic cases occur in the absence of *A. aegypti* (Soper et al, 1933). Obviously the infection cannot spread to the small communities near the edge of the forest when these are located in areas virtually free of any vectors of yellow fever. Such indemnity against vectors is not always enjoyed and Burke (1937) has described an outbreak of 201 cases occurring in the absence of *A. aegypti.* Danger from another source may arise when a patient infected in the forest, visits a community where aegypti mosquitoes are present, and an outbreak of this nature has been recorded (Walcott et al, 1937). Looking backward, one readily recalls epidemics of yellow fever in which the origin still remains unexplained. In 1925 Muller and Blaisdell reported 56 cases in San Salvador, far removed from any known focus of infection and without any recognized importation of

primary cases; the possibility of a sylvatic focus deserves some consideration, though there is no evidence that yellow fever exists in the forest regions of this country at the present time. West Africa presents some difficulties in epidemiological studies concerning sylvatic foci of infection but the results of investigations there will be awaited with interest, especially in view of the opinion that Africa is the original home of yellow fever. Some day, information may become available which might indicate whether yellow fever is essentially a disease of lower animals with periodic outbreaks in man or whether the virus has, possibly since its introduction to America, escaped from its cycle in man and the aegypti mosquito to establish itself in other species of vertebrates and arthropods.

Symptomatology

It is customary to state that the incubation time of yellow fever varies from 3 to about 6 days; in one instance a period of 13 days was noted by Marchoux et al (1903). There is much individual variation in the severity of the course of the disease with many gradations between the mild and the serious cases. To refer to the devastating epidemic of 1797 in Philadelphia, Rush (1798) emphasized that "There were cafes of this fever fo light that * * * such perfons walked about and tranfacted their ordinary bufinefs." In 1928, this observation was confirmed experimentally when the virus of yellow fever was recovered from patients who developed merely febricula of a few days' duration. During an epidemic, yellow fever patients present symptoms and signs which are almost clinically diagnostic in the severe cases. With slight prodromata, often during the night, the temperature rises moderately, the pulse and blood pressure increase, and the patient experiences chilly sensations, headache, rachialgia and the attending discomforts of fever. The characteristic signs of the infection begin to appear early in the course of the disease. Changes in the urine may occur late in the second or during the third day. Albumin is found at first only in traces, but it may increase so rapidly within a day or two that the urine almost clots on boiling. A tentative diagnosis of yellow fever is justified in these cases which show this rapid increase in the albumin content of the urine. Casts are usually found in abundance. The volume of urine tends to decrease and oliguria may become a serious factor.

The temperature remains only moderately high, but as the fever reaches its fastigium the pulse rate falls and this disproportion between the temperature and pulse is known as Faget's sign. The myocardial changes rather than the slight or moderate jaundice may, quite conceivably, be the significant factor responsible for the slowing of the pulse rate. Prostration is an outstanding feature and its severity seems out of proportion to the temperature and general condition of the patient. Well-marked prostration rather than the classical symptoms of yellow fever was an important feature in the clinical diagnosis of a moderately severe case in Senegal from which the French strain of virus was obtained.

Jaundice and evidence of haemorrhages may be expected as early as the fourth or fifth day of illness, though ordinarily the jaundice is not intense, even in severe cases. The gums tend to bleed easily on pressure and frank haemorrhages may occur in the stomach and intestine accompanied by epigastric pain. The stomach contents may consist chiefly of blood which almost invariably turns black, giving rise to the so-called "coffee-ground" vomitus, and the patients recognize that this ominous sign may foreshadow the end of their illness. Subcutaneous harmorrhages

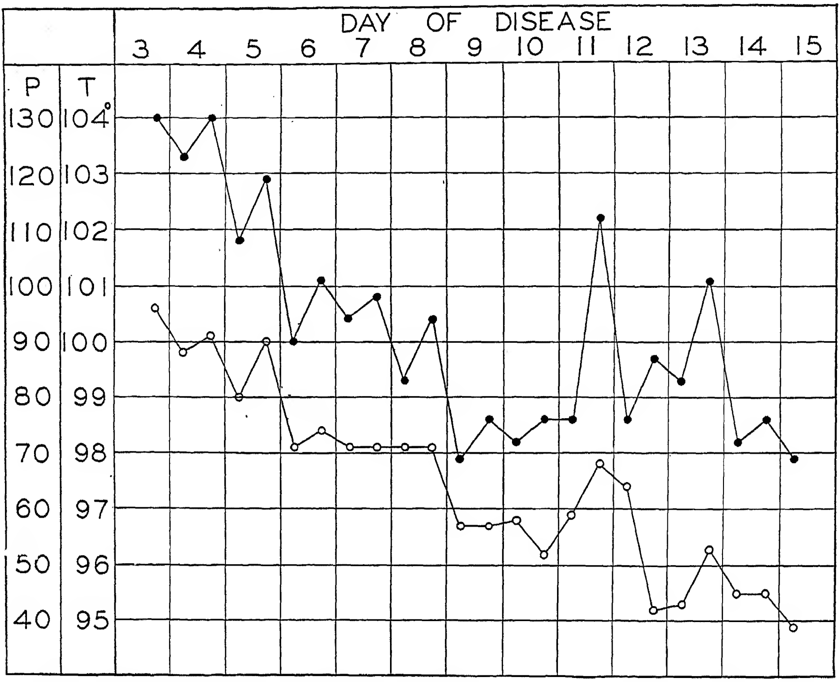

FIG. 201.—A moderately severe case of yellow fever with recovery seen in Guayaquil, Ecuador, through the courtesy of Dr. Wenceslao Pareja on the occasion of the expedition from the Harvard School of Tropical Medicine to South America in 1913. The pulse is moderately rapid early in the course of the disease but the rate shows progressive slowing as the infection reaches and passes its fastigium.

occur only exceptionally and they may appear as petechiae or as patchy ecchymoses. Patients tend to remain clear mentally and often become anxious and alert as the symptoms increase in severity. After a few days of illness the temperature falls in a small proportion of cases, the symptoms remit and a "period of calm" sets in, lasting at times only for a few hours, after which the temperature rises again, producing a "saddle-back" or "bactrian" chart.

Even during epidemics of exceptional severity, a considerable proportion of cases recover. Some of the higher estimates of mortality approach 75% or even 80%, but it would be difficult to obtain accurate data which include the mild cases that are difficult of diagnosis except

by the infection of experimental animals. Immune bodies develop rapidly and may co-exist with virus in the blood, but a fatal termination may ensue even in the presence of neutralizing antibodies. Under epidemic conditions, the majority of deaths occur during the first week of the disease, as illustrated by the accompanying table from Hanson's record (1929) of the Peruvian outbreak of 1921.

Table Showing Day of Illness on Which the Greatest Number of Deaths Occurred

Day of death	Number dying this day	Day of death	Number dying this day
2nd	4	12th	3
3rd	9	13th	3
4th	23	14th	2
5th	29	15th	1
6th	52	16th	1
7th	21	18th	1
8th	14	20th	1
9th	11	23rd	3
10th	7	24th	1
11th	8		

Relapses are rare and convalescence, when once established, ordinarily proceeds rapidly, without indication of any permanent damage to the myocardium and without any tendency to the development of complications such as a contracted kidney or cirrhosis of the liver. It is quite conceivable that no extensive destruction of hepatic parenchyma occurs in patients who recover and who show only a slight degree of peptonuria. This interpretation is distinctly at variance with the conclusions of Klotz and Belt (1930) who emphasize that complete and scarless healing of the liver and kidney occurs although these organs must have suffered appreciable damage after even a brief but typical attack of yellow fever.

Susceptibility of Man and Lower Animals

During an outbreak of yellow fever, there is evidence of much individual variation in the severity of the infection but the question of racial variation is admittedly difficult. The facts at hand do not permit final conclusions concerning all of the details that are involved, but the working basis for the epidemiologist is clear. In Africa, yellow fever has long been considered as a disease of the white race and the negro has taken little interest in control measures but the fallacy in this interpretation lies, in part, in the mildness of the symptoms sometimes observed in children though this feature has been somewhat over-emphasized. However, in endemic zones many of the native children develop unrecognized infections and as adults their immunity during an outbreak has been attributed to natural resistance. The error of this conclusion has been

illustrated quite clearly in our southern states where negroes growing up in this country appeared to enjoy no racial protection and the epidemiologist is confronted with the difficult task of finding and diagnosing mild cases instead of adopting the easy assumption of racial insusceptibility. The importance of the negro race in maintaining and spreading the infection was emphasized in Dakar, where the French authorities quite commendably called the first international conference for coördinating the efforts of various countries in the study and control of yellow fever (Conférence Africaine, 1929).

Extensive search has thus far failed to reveal natural infections in lower animals accompanied by typical signs and symptoms though the demonstration of protective substances in the blood of some species of monkeys presupposes inoculation of the virus attended at least by an inapparent reaction. The behavior of lower animals upon inoculation with the virus of yellow fever requires consideration of a wide range of susceptibility varying from entirely inapparent effects to the development of fatal infections which in some cases may be quite similar and in other circumstances quite different from the disease as it occurs in man. It will be sufficient to describe characteristic examples of the various types of reaction without a detailed discussion of each species.

The rhesus monkey (*Macaca mulatta*) develops symptoms and lesions that resemble closely the human disease (Stokes, Bauer and Hudson, 1928). Under the severe conditions of laboratory experimentation, the mortality of the monkeys is extremely high (95 to 100%), and, at times, nearly all of the parenchyma of the liver may be necrotic. The French strain of yellow fever was obtained in Senegal (Mathis, Sellards and Laigret, 1928), and, if so desired, its virulence may readily be maintained at such a high degree that virtually all the inoculated monkeys will run an acute and fatal course. Infective liver from a monkey dying of yellow fever was transported in the frozen state from West Africa to London and subsequently to the United States, this being the first strain taken out of Africa. Much of the experimental work on yellow fever in the Institutes of Europe and America has been conducted with this strain either in its ordinary or its neurotropic form. *M. sinicus* is less susceptible than the rhesus monkey and, curiously enough, the chimpanzee appears to be markedly refractory to yellow fever.

The marked neurotropism of yellow fever virus is readily demonstrated by the intracerebral injection of the white mouse whereupon a fatal encephalitis ensues but without necrosis of the liver. In the accompanying illustration one notes the rough hair, the kyphosis and, just posteriorly, the line of constriction resulting from interference with respiration. Paralysis of the hind legs and also of the tail is virtually complete. As a routine, virus is injected in the frontal lobe and becomes disseminated throughout the brain and cord. The frequency with which paralysis in yellow fever and in some other neurotropic infections appears first in the hind legs under these conditions has not been fully explained by the neurologists. Theiler, at the Harvard Medical School (1930), established

a neurotropic strain by repeated intracerebral passage of the virus in mice, the neurotropism becoming somewhat enhanced but with a loss of the ability to produce serious hepatic lesions in the monkey or in man. With repeated passage of the virus in mice the course of the disease is shortened and death may occur as early as the fifth or sixth day. The intraperitoneal injection of white mice with unmodified virus produces a fatal encephalitis in a small proportion, some are immunized, and others remain susceptible (Sellards, 1935 a). At the suggestion of Andervont, new-born mice were injected intraperitoneally with ordinary virus and a fatal encephalitis developed just as in the adult mice injected directly

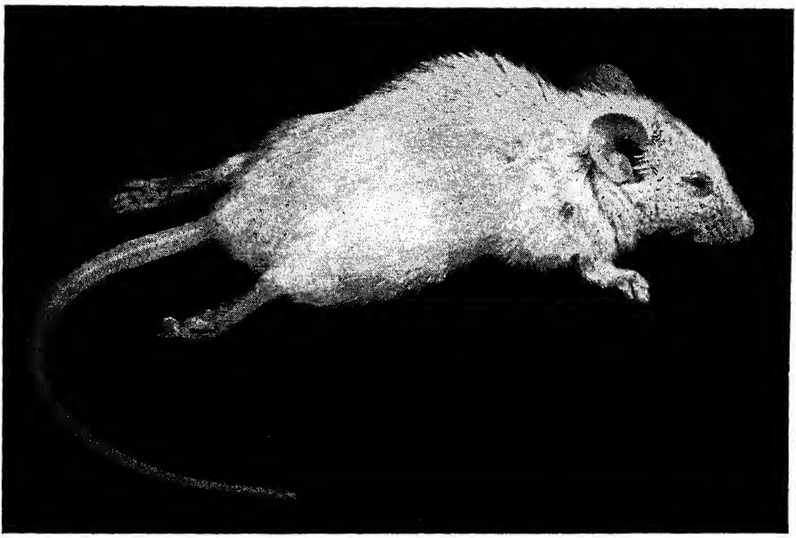

FIG. 202.—Encephalitis in a white Swiss mouse developing on the seventh day after intracerebral injection of the virus of yellow fever from the 404th passage in mice.

into the brain. Encephalitis follows the intracerebral injection of various rodents and several species of monkeys which remain well after ordinary routes of injection.

The monkey (*M. mulatta*) reacts in an interesting manner with regard to the intracerebral and the extraneural injection of the virus of yellow fever in its ordinary and its neurotropic modification (Sellards, 1931). After intracerebral injection of neurotropic virus, a fatal encephalitis usually ensues without jaundice or hepatic lesions, whereas the subcutaneous injection of the neurotropic modification produces, as a rule, only a mild infection with immunity. The ordinary virus, though it possesses marked neurotropic affinities, fails to produce encephalitis upon intracerebral injection, but the animals die in a few days with necrosis of the liver before there is adequate time for the development of the cerebral lesions. An important observation has been contributed by Penna (1936) who immunized rhesus monkeys passively with a potent serum and then

injected them intracerebrally with yellow fever virus in its ordinary form. Under these circumstances, encephalitis developed but the immune serum protected the liver from any extensive degeneration.

There are a considerable variety of species which develop only an inapparent infection when inoculated extraneurally with the ordinary virus of yellow fever. Thus, in the guinea pig, the virus was transferred serially from one animal to another at intervals of 5 to 7 days by intraperitoneal injection without the development of symptoms or lesions.

THE USUAL BEHAVIOR OF THE ORDINARY AND OF THE NEUROTROPIC VIRUS OF YELLOW FEVER IN VARIOUS ANIMALS

Virus of yellow fever	Route of injection	Animal	Lesions		Result
			Liver	Brain	
Ordinary	Extraneural	Monkey (*M. mulatta*)	Necrosis	None	Death
	Intracerebral		Necrosis	None	Death
Neurotropic	Extraneural		None	None	Inapparent infection and immunity
	Intracerebral		None	Encephalitis	Death
Ordinary	Extraneural	White mouse	None	None[1]	Susceptibility or immunity[2]
	Intracerebral		None	Encephalitis	Death
Neurotropic	Extraneural		None	None[1]	Susceptibility or immunity[2]
	Intracerebral		None	Encephalitis	Death
Ordinary	Extraneural	Guinea pig	None	None	Immunity
	Intracerebral		None	None	Immunity
Neurotropic	Extraneural		None	None	Immunity
	Intracerebral		None	Encephalitis	Death
Ordinary	Extraneural	Hedgehog	Necrosis	....	Death
Neurotropic	Extraneural		Necrosis	Encephalitis	Death
	Intracerebral		Necrosis	Encephalitis	Death
Ordinary	Ingestion	Mosquito (*A. aegypti*)	....	None	Virus multiplies

[1] *Small percentage of encephalitis.*
[2] *Some remain susceptible, and some are immunized.*
From the Symposium on Virus and Rickettsial Diseases (1940), *by courtesy of the Harvard University Press.*

Some blood and spleen from a guinea pig of the third passage was injected nto a monkey and death from yellow fever occurred on the third day (Sellards, 1930). The neurotropic strain upon intracerebral inoculation produces a fatal encephalitis in guinea pigs (Stefanopoulo and Wassermann, 1933). Several species of animals, notably cebus monkeys, the ferret, the rabbit and the hen, develop a protective serum when injected with the virus in its ordinary form (Sawyer and Frobisher, 1930), and

the infection of chick embryos has been described by Jadin (1937) and by Elmendorf and Smith (1937). The data concerning the more important types of reaction are illustrated in the table on page 888.

Various species of arthropods may harbor the virus of yellow fever without transmitting the infection when feeding on a susceptible animal, but only when crushed and injected subcutaneously in monkeys or even intracerebrally in mice. The many species of mosquitoes which serve experimentally as a vector show no injurious effects from the presence of the virus. Relatively little has been added to the basic facts reported by the United States army commission in 1900 concerning transmission by the aegypti mosquito. Virus may be demonstrated in mosquitoes at any period after an infective feeding by grinding and injecting the insects into a monkey (Davis and Shannon, 1930) and there is no indication of any developmental cycle. The optimal temperature for the growth of the virus may be determined with considerable accuracy by noting the incubation time required at different temperatures before the bite of the infected mosquito becomes dangerous. Briefly, one could be bitten with impunity by infected mosquitoes kept continuously at 10° to 15°C. (Hindle, 1930), but at 37°C. the incubation time is shortened to a few days, just as in man, instead of the classical period of about 12 days at room temperature (Sellards, 1930). This experiment justifies the conclusion that the virus multiplies in the mosquito (Sellards, 1935) and additional confirmation was supplied by Whitman (1937) who used other methods of experimentation. Valuable data concerning the effect of temperature on the incubation time in the aegypti mosquito were supplied by Davis (1932) but with the erroneous interpretation that no multiplication of the virus takes place in this host (Davis, Frobisher and Lloyd, 1933). Precise information is lacking in regard to the exact nature of the events that take place during the incubation period. The rather unwarranted assumption has been offered that the virus injected by a mosquito must of necessity come from the salivary glands. In dissecting these glands to test their infectivity, they may easily be contaminated with tissues of the mosquito known to be rich in virus. In a few experiments we found no virus in traces of coelomic fluid drawn off by thoracentesis from infected mosquitoes. There is no evidence of any specific microörganism nor any reaction or lesion in the tissues and even serial sections fail to distinguish infected from normal mosquitoes.

Technical Procedures

The customary bacteriologic technique should afford adequate protection for working with animals infected with yellow fever. Virulent strains induce a rapidly fatal disease in the rhesus monkey though quite exceptionally, some individuals remain apparently well for a few weeks and then die suddenly, the anatomical lesions being typical of yellow fever with no indication of any chronic process. Occasionally, some monkeys show no definite febrile reaction but develop a significant degree of malaise and death may occur within 3 or 4 days after inoculation.

Fortunately, the maintenance of a strain of virus in the laboratory does not require continuous passage in animals since infective tissues retain their virulence when frozen (Sellards and Hindle, 1928). As a routine procedure it is neither necessary nor advisable to dry the frozen tissue, some laboratory infections having been attributed to accidents in handling virus, in the form of a dry powder.

The mosquito *A. aegypti* lives by preference in the home, and with but little change in its usual habits colonies may be maintained readily in the laboratory. On no occasion do we follow the practice of introducing a monkey into a cage of mosquitoes. On the contrary, the animal is held outside of the cage against the wire screen and the mosquitoes bite readily through the meshes. The special trap illustrated in the accompanying figure permits the removal, with perfect safety, of a few mosquitoes from a cage of infected ones in case some are desired for special study. The manipulation of this trap is altogether simple and its use has been described in detail (Sellards, 1932).

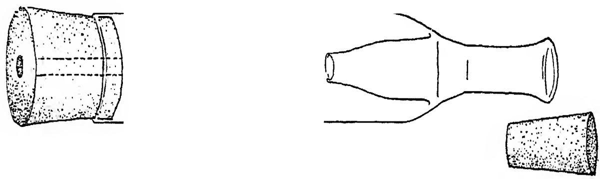

FIG. 203.—Trap for handling infected mosquitoes (½ actual size). (Reproduced by courtesy of the Waverly Press, Baltimore.)

Protection Tests.—By exact experimentation on man, Marchoux, Salimbeni and Simond (1903) demonstrated that the virus of yellow fever is neutralized by the serum of convalescent patients. In a similar manner, the protection of rhesus monkeys was demonstrated soon after the discovery of the susceptibility of this species. Hindle (1930) noted the protection of monkeys by the serum of a patient 24 years after recovery from yellow fever there being no opportunity for re-exposure during this long period. Theiler (1930) substituted mice for monkeys, using intracerebral inoculations. This severe route of injection permits the use of only minimal amounts of serum. Nevertheless, this method with some modifications proved quite satisfactory for testing the protective action of the serum of persons vaccinated against yellow fever (Sellards and Laigret, 1932 c). A valuable modification of the test was introduced by Sawyer and Lloyd (1931), the injections of serum and virus being made intraperitoneally, with traumatization of the brain by the injection of starch paste to facilitate localization of the virus. Liberal amounts of infective mouse brain are triturated and injected but it seems preferable to centrifuge the suspension and use only the supernatant fluid (Sellards and Bennett, 1937). Mice dying on the 4th or 5th day of neurotropic yellow fever are sacrificed and a 15% or 20% suspension of a highly infective brain is prepared in physiological saline containing 10% of normal serum. The tissue is removed by centrifuging, the super-

natant fluid is rich in virus and the control mice will die with regularity. Starch paste or distilled water is injected intracerebrally in mice in groups of 6 for each serum to be tested, this being a convenient number originally adopted by Theiler. Then equal parts of the suspension of virus and of the serum to be tested are mixed and injected intraperitoneally without preliminary incubation, using 0.5 cc. of the mixture. The majority of the mice which are not protected die about the 6th or 7th day, though quite exceptionally an occasional death may occur even in the third week after injection.

The specificity of the protection test in mice has received critical examination through a period of years by reason of the many thousands of human sera that have been examined in outlining the endemic zones of yellow fever. There are only a few instances of apparently "false" reactions where protection has been afforded by the serum of a person who could in no way have been exposed to yellow fever. Peltier et al (1937) have advised caution in the interpretation of tests made with sera containing bile pigments and bile salts, since the virus of yellow fever is sensitive to the action of bile. The specificity of the test when applied to lower animals requires individual consideration of each species. Attention is invited to the protection afforded by normal serum of sheep (Findlay et al, 1936, and Smith, 1940).

A survey of immunity in the various age groups of a given population may enable one, under favorable circumstances, to reconstruct the history of yellow fever in the community with considerable exactness. This may be illustrated readily by an instance where one is able to compare the historical data with the results of an immunity survey. Thus one may be able to distinguish between active foci of infection and others which have become extinct, such as the endemic zone which formerly existed in Cuba. The last outbreak in this island occurred in 1905 and persons born after that date have no immunity to yellow fever as determined by protection tests.

Modification of Yellow Fever Virus

The virus of yellow fever has been modified not only by intracerebral passage in mice but also by continuous cultivation *in vitro* in surviving tissue. In either case there is a loss of the ability to produce hepatic necrosis but with persistence of the neurotropic properties. The interpretation that these two characteristics can be varied at will by laboratory procedures requires some qualification since no strain has been developed which produces typical symptoms of yellow fever in the rhesus monkey with failure to cause encephalitis in mice. Actually the essential feature is uniformly in the direction of a loss of the tendency to destroy the liver parenchyma, with occasional reports of reversion to the natural virus. The neurotropic virus is not obligately neurocytotropic but it multiplies on subcutaneous injection in man, and virus appears in the blood stream (Sellards, 1937). The ordinary virus of yellow fever has been designated by various terms such as "viscerotropic" and "pantropic," but viruses

are characterized by an affinity for certain types of cells rather than for the various viscera and the significance of tropism is lost when applied as a "pantropism" for all cells. Precise terminology for the ordinary strain must await further developments but the phrase "natural virus" of yellow fever (Lloyd and Mahaffy, 1936) is unmistakably clear and satisfactory. Unexpected confusion has arisen in the consideration of some of the modified strains. Findlay (1934) suggests that the neurotropic virus maintained in mice should, in fact, be regarded as pantropic since it is not strictly neurotropic. In another instance, a modified "viscerotropic" virus proved on examination to be a strain which after long cultivation by Maitland technique fails to produce visceral lesions, but continues to cause a fatal encephalitis on intracerebral injection. Briefly, this conforms to the prevailing conception of a neurotropic strain.

The ordinary virus cultured for three years *in vitro* on surviving tissue gave rise to the modification designated in the literature as "17 D." On intracerebral injection in monkeys this strain produces an encephalitis followed by recovery, but in mice a fatal encephalitis occurs in about seventeen days. There is, therefore, no doubt about the neurotropism of the culture known as 17 D and in the subsequent section on vaccination it is designated for the sake of clearness as a cultural neurotropic modification. The changes which the ordinary virus undergoes upon cultivation *in vitro* are of much interest and the mechanism of these changes seems obscure. Gordon (1940) concluded that the type of tissue used for cultivation determines the nature of the changes but the evidence is unconvincing.

There is room for difference of opinion concerning the possible reversion of neurotropic to the ordinary form of virus of yellow fever. First of all, it is important to note that none of the modifications have been maintained for long periods comparable, for example, to the many years that the fixed virus of rabies has been transferred from rabbit to rabbit. The French neurotropic strain of yellow fever, after about 200 passages in mice, was injected into the liver of rhesus monkeys and the strain regained its original properties, according to the observations of Findlay and Clarke (1935). This result is of much theoretical importance and deserves confirmation. Findlay and MacCallum (1938) reported spontaneous reversion of the neurotropic strain, and this important observation also awaits confirmation. In one instance, the injection of a baboon with neurotropic virus was interpreted by van den Berghe (1939) as resulting in reversion of the virus to its ordinary form, but a final conclusion may be left to await a critical review of the criteria employed for describing and determining reversion. In practical experience with vaccination over a period of eight years no difficulties have arisen from reversion of neurotropic virus to its natural state.

An interesting protective action has been described by Hoskins (1935) who noted that rhesus monkeys survived when injected with both neurotropic and with ordinary virus, whereas controls injected with only

ordinary virus died. This is of especial interest since the ordinary virus is highly neurotropic.

In nature, strains of yellow fever from various sources appear to be reasonably constant in their immunizing power but show variation in their virulence for the rhesus monkey. No virus infections are known which show any close relationship to yellow fever in the sense of any overlapping in immunological reactions. In this respect dengue fever has attracted much attention, more especially because of its môde of transmission by *A. aegypti*. The careful investigations of Snijders, Postmus and Schüffner (1934) failed to show any immunological relationship or any indication of etiological similarity between dengue and yellow fever.

Vaccination

Specific prophylaxis against yellow fever was regarded, at one time, as quite unnecessary or even undesirable since prevention of the breeding of aegypti mosquitoes appeared to afford an efficient and almost an ideal method for the control of epidemics. However, in each outbreak many lives are lost during the weeks and even months that elapse before the measures against the mosquito become effective and no practical methods are available, as yet, for avoiding or controlling the vectors in sylvatic regions.

The virus of yellow fever behaves in a manner that simplifies considerably some of the problems involved in the development of an appropriate method of vaccination. Even a mild infection results in a substantial and lasting immunity. For practical purposes it is fortunate that strains of virus from widely separated regions afford mutual cross protection (Theiler and Sellards, 1928). Immunization with lifeless vaccine is only in the experimental stage (Findlay and MacKenzie, 1936). Repeated injection of rabbits with non-infective virus resulted in a measurable degree of immunity (Sellards and Bennett, 1937), the results being improved by the addition of cysteine for the protection of the labile antigen (Mudd et al, 1937).

In practice, one injection of living virus is used for the immunization of man with the expectation of producing a mild or inapparent infection. A method for mass vaccination for the control of yellow fever was developed in 1932, using a neurotropic virus maintained by intracerebral passage in mice (Sellards and Laigret, 1932 a–b–c). Investigation of the effect of neurotropic virus on man was approached with caution using preliminary injections of lifeless vaccine followed by the subcutaneous injection of an extremely high dilution of infectious mouse brain. No local or general reaction developed either to this injection or to subsequent inoculations of increasing amounts of living virus, but an immunity developed as indicated by successful protection of mice using the severe intracerebral route for the injection of virus mixed with minimal amounts of serum. The margin of safety of this procedure for vaccination of man was tested in one instance by using a moderately low dilution of virus for the initial injection. There were no appreciable subjective symptoms

but the temperature rose to 38° on the sixth and seventh days, accompanied by a bradycardia with a trace of albumin in the urine. The first tests on a large scale were conducted with a cautious plan of using 3 injections at intervals of 20 days. In Senegal, more than 3,000 volunteers were vaccinated in this way in the summer of 1934 by Laigret who emphasized that two of these volunteers developed serious symptoms of myelitis and meningitis followed by complete recovery. By the end of the summer of 1935 the vaccinations in French West Africa had reached 23,890 injections, the greater part of these representing three inoculations for each individual (Mathis et al, 1936). The next step in simplification of the technique consisted in suspending the virus in egg yolk to delay its dissemination and using only one injection of vaccine (Nicolle and Laigret, 1935).

The efficacy of this method of vaccination has been established by the results of its practical application in endemic zones of yellow fever and by experimental investigations. Small amounts of the serum of vaccinated persons protect monkeys and mice against excessively large quantities of virus. This protective action affords suggestive evidence but not exact proof of the immunity of the individual. However, a member of the staff, nearly eight months after routine vaccination, developed no reaction when bitten by infected mosquitoes, though normal monkeys bitten by these mosquitoes died of yellow fever (Sellards and Laigret, 1936 a–b). This demonstration influenced favorably the Commission of the Société de Pathologie Exotique in Paris in recommending voluntary vaccination for communities in Africa exposed to yellow fever (1936). The demand for protective immunization was urgent and there was no need to make vaccination compulsory. The following unpublished observation illustrates the persistence of protection over a long period. An individual who received one injection of infective mouse brain experienced almost no symptoms, but five years later his serum in a dilution of 1 to 50 protected 5 of 6 mice against yellow fever, using the intraperitoneal route of injection. Peltier (1938) summarized the results of 4 years' experience in vaccination for the control of yellow fever in French West Africa, and he recommends attenuation of the quarantine procedures for those who have been successfully protected. Tests were made at varying intervals to determine the duration of immunity, the longest period being 3 to 4 years after vaccination. The serum of 31 cases was examined at this interval and 26 afforded strong protection for mice whereas 4 gave feeble protection and 2 resulted in failure. A sufficient period of years has not yet elapsed for determining the maximum duration of the immunity that may follow this method of vaccination. In working on a large scale, occasional failures are to be expected. One of the 3,000 volunteers vaccinated in Senegal in the summer of 1934 developed yellow fever two years later in an endemic zone in Africa and the infection terminated fatally.

The cases with symptoms of involvement of the central nervous system have been reviewed in full by Laigret (1936). Opinions differ concerning

the nature of these reactions. The virus of yellow fever was not recovered from the blood or spinal fluid of any of these cases but it may quite conceivably have been present in the central nervous system. In one patient a complicating infection was due to the virus of lymphocytic choriomeningitis which evidently was present in the mouse from which the vaccine had been prepared (Laigret and Durand, 1936). The literature emphasizes one fatality but this occurred after an interval of one year and two months without definite evidence of any relationship to the vaccination.

Peltier et al (1940) have introduced a technique of exceptional interest which consists in scarifying the skin with a mixture of virulent neurotropic yellow fever virus and the virus of vaccinia, no severe reactions being observed even in infants. The simplicity of the method permits its rapid application and 98,873 persons have been vaccinated in this way. Protective substances against yellow fever developed in the serum of 95.6% of 1,387 cases, the serum being strongly protective in 80.6%.

The neurotropic strain of yellow fever is not readily transmitted by aegypti mosquitoes (Sellards, 1931), though occasional successful results have been reported experimentally (Davis et al, 1932). During the course of vaccination, virus may be present in the circulating blood and Sawyer with his associates (1932) have discussed the possibilities of an outbreak of yellow fever originating from vaccinated persons. There is no reason to suppose that transmission of virus by mosquitoes has occurred during the many vaccinations that have been practiced in Africa and there is no indication that the neurotic strain tends to revert in the mosquito to the ordinary virus.

A complicated process described as serovaccination was investigated by Sawyer and his associates (1932) for the protection of their staff, many accidental infections having occurred among their laboratory personnel. In principle, the injection consists of liberal amounts of neurotropic virus which is underneutralized with specific immune serum. Ordinarily a mild infection results and the serum shows neutralizing bodies for a period of a year or so. Serovaccination has only a limited field of application and the procedure is accompanied by some risk of complications involving the central nervous system (Darré and Mollaret, 1936). A similar case of encephalitis following serovaccination was noted by Sawyer (1937). Jaundice of unknown etiology developed within two to eight months in 20% to 30% of a group of persons receiving serovaccination (Soper and Smith, 1938). The use of neurotropic virus without immune serum has been opposed more especially by Findlay (1934) in England, and by Theiler and Whitman (1935) in this country, though no other plan of mass vaccination was available and they do not report any experience with its application in man. Gordon and Hughes (1936) cite Theiler and Whitman as questioning the safety and quite erroneously state that Findlay (1934) questions the efficacy of vaccination by neurotropic virus maintained in mice. It would seem paradoxical to consider that a severe reaction in yellow fever would, nevertheless, fail to produce immu-

nity. However, Gordon (1940) again cites Findlay as questioning the immunizing effect of the virulent neurotropic strain, although he accepts readily the effectiveness of this strain when its activity is impaired by using liberal amounts of specific immune serum and unhesitatingly recommends a cultural neurotropic strain of feeble virulence (17 D) as providing an effective vaccine.

Much attention has been given to vaccination with neurotropic strains of rather slight virulence maintained by culture *in vitro* or surviving tissue, and by infection of chick embryos. Findlay and MacCallum (1937) vaccinated 65 persons with a cultural "pan-tropic" strain without immune serum. The description of this strain indicates that it is a neurotropic modification. A few months later, Theiler and Smith (1937) reported, quite independently, the experimental immunization of 8 persons with neurotropic cultural virus (17 D) but without the use of immune serum. Subsequently, Smith et al of the Rockefeller Foundation adopted mass vaccnatiion in 1938 as a means of controlling yellow fever. They inued the use of immune serum and prepared a vaccine from chick with cultural neurotropic virus. This strain upon inocu induced the formation of antibodies but frequently the titer of the serum was low and a fall in titer was note within 6 to 10 weeks after vaccination. The Coöperativ Service of Brazil reported the vaccination of more than 59,000 persons with the probability that under field conditions approximately 95 per cent of these were immunized. One instance was noted in which encephalitis occurred as a complication, followed by complete recovery (Soper and Smith, 1938). The use of vaccine was extended rapidly and 305,000 persons were inoculated in the state of Espirito Santo in Brazil (Soper et al., 1940). Some unfavorable results appeared. Among 156,000 vaccinated persons, 56 cases of yellow fever were reported with 14 fatalities. Unquestionably these infections were acquired naturally and were in no sense attributable to the injection of virus without immune serum. Protection tests in some groups indicated that 50 per cent to 80 per cent remained susceptible after vaccination. Cultural strains of yellow fever do not remain fixed in their pathogenicity and in their immunizing

Choice of Virus.—Successful vaccination against yellow fever depends on the injection of living virus with the development of an infection. The modified virus suitable for inoculation in man is neurotropic in character, and, fortunately, two strains are available. The one propagated in mice is virulent and produces an enduring immunity with the risk of a small proportion of serious reactions. The cultural strain is of low pathogenicity and uncertain in its immunizing effects, with the risk that individuals supposedly protected by vaccination may contract yellow fever. In the emergency of an epidemic effective protection may be quickly obtained by mass vaccination with virus from infected mice. A technician could easily prepare within an hour sufficient vaccine for a million persons. In epidemic zones, the populace will readily accept a

slight risk for the assurance of adequate protection but a method which from time to time leads to a sense of false security tends to undermine the confidence of the community. The cultural strain is especially useful for exceptional circumstances where individuals remain under observation, the results being determined by protection tests with repetition of the injections till immunity is established. Neurotropic variants of yellow fever are under investigation in several laboratories for the purpose of obtaining still further improvements in the technique of vaccination. Peltier et al (1937) have investigated the immunizing effect of neurotropic virus mixed with minimal quantities of bile.

The criteria for the ideal method of vaccination against yellow fever have been defined by various authorities, emphasizing the welfare of the individual, and also the danger that the reaction developing during immunization might accidentally set up an epidemic among the unvaccinated. It would seem within reason that a person volunteering for vaccination should expect to obtain adequate protection and also expect that the resulting immunity might endure at least for the brief period of a few years. Much progress has been made in this direction in a rather brief period of time but one hopes and expects that distinct improvements will be made in any of the techniques which are in use at present for mass vaccination.

Prevention

The protection of communities involves consideration of the familiar aegypti-borne epidemics of cities and the more obscure problem of sylvatic yellow fever. After many years of experience, reasonably effective methods have been developed for the control of aegypti mosquitoes, but the details of the procedures vary widely according to the local conditions. *A. aegypti* is highly domestic, living by preference in homes and feeding on man. An adequate municipal water supply works to the great disadvantage of the mosquito, since the householder can then do away with favorite breeding sites such as the many jars and vessels used for storing potable water. In times of necessity the mosquito shows much ingenuity in finding water for depositing her eggs, such as the small amounts that collect in a flower pot or air plant or a discarded can. The development from ovum to imago requires about two weeks and many larvae and pupae might die in case a small residue of water evaporated within a few days. The mosquito quite carefully, as a rule, lays her eggs not on the water but just above the water line; the eggs withstand drying and adhere to the container. Some days or weeks later, when the containers are filled by a shower, larvae appear within a few minutes, insured of a more liberal supply of water for their development. About 2 weeks after a drought has been broken, it is a common experience that mosquitoes may appear in and around homes in annoying abundance.

During inter-epidemic periods, the imagos may be ignored and the mosquito population in cities can be reduced to a minimum by thorough destruction of larvae and pupae at weekly intervals. Small vessels of

water containing larvae may be emptied in seasons when rainfall is abundant. In arid regions, sanitary inspectors discarding small quantities of much needed drinking water have met with serious experiences and it is sufficient to remove the larvae by straining the water through a piece of cloth. Shallow wells, cisterns, tanks and similar containers may be protected more or less effectively by screening, oiling, or the use of small species of fish which feed on larvae. The ingenuity of aegypti mosquitoes in finding breeding places and the difficulty in some circumstances of locating the adults requires some caution in accepting the conclusion that any given outbreak of yellow fever is occurring in the absence of aegypti mosquitos. During an epidemic of yellow fever the measures for the control of larvae should be broadened to include destruction of the adult mosquitoes. Fumigation of houses where cases have occurred is time-consuming, but this precaution may destroy some infected mosquitoes and also build up the confidence of the people and encourage their coöperation. The individual patient should be protected by screening or a bed net for his own comfort throughout the course of the illness and not merely for the first few days, thereby avoiding any necessity of explaining to the laity the scientific details concerning the môde of transmission. Prophylaxis for the individual consisted formerly in avoiding mosquitoes, but vaccination now constitutes the method of choice allowing a period of a few weeks after inoculation to elapse before exposure to yellow fever. In case of exceptional emergency, immediate but temporary protection can be secured by passive immunization with liberal amounts of a potent immune serum. For the purpose of quarantine, a period of isolation for 6 days has been adopted and this has proved reasonable in practice and preferable to more stringent measures of endeavoring to cover the exceptional maximum limits of incubation. The replacement of sailing vessels by steamships virtually eliminated the transfer of yellow fever to and fro across the Atlantic Ocean. The development of air services offers new problems of interest to the epidemiologist, but the aviation officials coöperate willingly and effectively with the health authorities. Our southern border lies but 10 or 12 hours distant by aeroplane from potential foci of yellow fever in South America. In British India all air traffic from the west arrives at Karachi and the airport there has been made "anti-amaryl," the Government taking every precaution to prevent the introduction of the virus, either in patients or infected mosquitoes (Russell, 1939).

The lack of detailed information concerning the hosts and vectors of sylvatic yellow fever precludes the adoption of any effective measures for controlling this infection in the wild life of the forests. For man, vaccination constitutes the only practical measure for protection.

Diagnosis

As indicated by the symptomatology, the clinical diagnosis of severe cases during an epidemic is relatively simple and accurate. The features are not pathognomonic but the acute onset with headache and backache,

the rapidly developing albuminuria, the extreme prostration, the usual Faget's sign, a moderate degree of jaundice and vomiting with or without haemorrhage constitute a characteristic syndrome. A progressive leukopoenia occurs at the expense of the neutrophiles and reaches its lowest point near the end of the first week of illness (Berry and Kitchen, 1931). Except for those patients who show an early and extreme degree of albuminuria, there are no methods available either in the clinic or the laboratory for establishing even a tentative diagnosis during the first few days of illness. However, this is the period of maximal infectivity of the blood and it is the appropriate time for commencing simple laboratory procedures which eventually should lead to a conclusive diagnosis preferably by the infection of susceptible animals or by the demonstration of neutralizing substances specific for yellow fever.

The white mouse rather than the monkey appears to be the animal of choice, successful infection with yellow fever by the intracerebral injection of patient's blood having been accomplished by Mathis in 1937. In the same manner Durieux (1937) in an important communication reports the infection of white mice with the blood from 13 patients, the virus being demonstrated in the patient's blood as late as the fifth day. Death of the mice about 10 days after inoculation with characteristic paralysis and without bacterial infection affords strong presumptive evidence of yellow fever; confirmation of the diagnosis may be easily determined by protection tests with yellow fever immune serum. If no virus is recovered from the patient's blood, then protection tests may afford an exact diagnosis provided that 2 specimens of serum are examined, one of which is taken during the first few days of illness and the other after an interval of 3 or 4 weeks. The first specimen shows either no protective power or else a low titer as compared with the second sample. The early development of immune bodies complicates diagnosis by this immunity test. Moreover, the first specimen of serum may contain neutralizing antibodies in high titer as the result of a previous infection with yellow fever, the current illness being due to some other type of acute infectious jaundice. In case of a fatal outcome, the lesions of the liver are virtually pathognomonic. Zenker's fluid is the fixative of choice, but in circumstances where this is inconvenient formalin serves as a useful substitute.

Differential Diagnosis.—Difficulties in clinical diagnosis arise in mild infections and also in those of moderate severity with well-marked symptoms. In the early days of the infection the fever, rapid pulse, malaise, albuminuria and leucopoenia resemble the symptoms at the onset of a case of influenza without respiratory signs. The mild types with no jaundice may be confused with those cases of dengue fever which show no rash or one so evanescent that it escapes detection. Quite exceptionally, cases of dengue fever have been said to show slight jaundice discernible as a tingeing of the sclerae. These observations were made before the laboratory diagnosis of yellow fever had been developed and similar methods for dengue fever have not yet been perfected. Of the

severe and even fatal types of acute infectious jaundice, much confusion has arisen between yellow fever and leptospiral jaundice (Weil's disease) and this confusion persisted for some years after the introduction of reliable laboratory methods for the recognition of leptospiral infection. Briefly, the guinea pig is the animal of choice for inoculation with infective blood or urine of patients or for a protection test using virulent leptospira and convalescent serum. The severity of leptospiral infection varies through all gradations from a febrile reaction lasting for a day or two without jaundice to a mortality of as much as one-third of the cases. In its severe form, the jaundice may be more intense than in yellow fever but the albuminuria is less marked. There are several other minor distinctions but the final conclusion rests upon the laboratory findings. Cases of relapsing fever and malaria fever may occasionally show some jaundice. In regions where malarial infection is prevalent, it is customary to emphasize the precaution that the finding of malarial parasites does not exclude infection with yellow fever.

Prognosis

The condition of patients whose progress appears to be satisfactory may without warning become altogether critical, and this insidious nature of the infection requires especial caution in predicting the course of the disease. After long experience, Dr. E. J. Scannell suggests that a good prognosis may be offered with certainty only when the patient is out of bed, and dressed, and out of the house and walking down the street. There are many features of unfavorable portent, notably haematemesis, melena, extreme malaise, suppression of urine and peptonuria. Rush (1798) listed 21 unfavorable signs, among them "a preternatural appetite, more efpecially in the laft ftage of the fever," and this observation becomes of significance in view of the low values for blood sugar following injury to the liver. In summarizing the temperature records of 269 patients, Sternberg (1890) noted that 22 with a temperature of 106° or higher ended fatally, and 44 cases whose temperature did not exceed 103° had the good fortune to recover, the mortality for the group being 27.5 per cent. The mildness of the disease in children has been somewhat overemphasized. Some fatal infections occurred in infants during the outbreak of 1927 in Parahyba, Brazil. Hanson (1929) in a severe epidemic in Perú noted a mortality of 83 per cent in children of 1 to 3 years of age, and 34 per cent in a group from 6 to 10 years old.

Therapy

General Measures.—Rest in bed is altogether essential, even in supposedly mild infections. It is much better that a patient taken ill in unfavorable surroundings should be made reasonably comfortable rather than to take the very real risk of transportation to a more suitable environment. A purgative is appropriate to relieve constipation at the onset of the disease with preference given to enemata when the more

serious symptoms develop. The gradual loss of fluids and the imbalance of inorganic salts as indicated by studies of urine suggest the use of some form of Ringer's solution. The impairment of renal function with suppression of urine is more serious than one would expect from the lesions seen in the kidney. In terminal stages, an accumulation of undetermined acids results in a reduction of serum bicarbonate (Wakeman and Morrell, 1932). Sternberg (1890) recommended Vichy or alkaline mineral waters or the administration of small daily amounts of sodium bicarbonate, such as 15 grams, to liberal amounts of drinking water. The disturbing gastro-intestinal symptoms may be controlled more or less effectively by the use of atropine.

Special Measures.—In the acute stage of yellow fever the custom prevails of prescribing an almost starvation diet supplemented by citrus juices when the patient is able to retain them. In contrast to this practice, the injury to the liver with impairment of glycogenic function, and the frequency of hypoglycaemia requires the liberal use of glucose especially by intravenous injection. The administration may be guided by sugar determinations in case the facilities of a chemical laboratory are available. Remarkable results are not to be expected but this treatment adds to the comfort of the patient and constitutes a rational supportive measure. The possibility of guanidine intoxication must be kept in mind. The metabolism of guanidine substances following injury of the liver has been investigated extensively (Lamson, Minot and Robbins, 1928; Minot and Cutler, 1928–1929; Minot, 1939). The administration of calcium relieves guanidine intoxication in a striking manner, not by destroying guanidine but by neutralizing its toxic effects. Calcium lactate in doses of 5 grams daily is suitable for oral administration, and calcium gluconate in 7.5 per cent solution may be given in 10 cc. amounts by intramuscular but not by intravenous injection. In principle, fluids should be supplied liberally, the carbohydrate reserve should be protected, alkalies are to be used in small amounts with discretion, and the administration of calcium should prevent any symptoms of guanidine intoxication.

Specific therapy is not available at present. Immune serum of high titer, even in large amounts, is inefficacious after fever has developed and it is better not to disturb the patient by such injections.

(For addendum 1942, see p. 904.)

References

Note: Owing to the limitations of space, about 45 of the references cited in the text have been omitted from the following bibliography, but many of these are available in the chapter by Sellards on yellow fever in the Symposium of the Harvard School of Public Health, on Virus and Rickettsial Diseases (1940). (R.P.S.)

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Addendum.—Since the preparation of this chapter upon yellow fever Findlay has reported upon the distribution of the disease in Africa and has published two maps showing the changes that have occurred. In one of these is indicated areas in which actual cases of the disease have been recorded between 1921 and 1941. In the other are shown the areas in which positive results have been obtained with immunity tests to yellow fever. The areas in the latter map are much more numerous and more widely spread. More recently (toward the end of 1940) the most extensive epidemic of yellow fever recorded in Africa has occurred in the Nuba Mountain region of the Anglo-Egyptian Sudan in which over 15,000 cases with 1,600 deaths were reported. There is evidence that the infection may have been present in the Sudan for a long time since mouse protection tests have given positive results in every region where they have been employed.

Findlay, Kirk and Lewis (1941) have emphasized the difficulty in diagnosing yellow fever in the field by clinical means and that this has been well illustrated by the occurrence of two epidemics not of yellow fever but associated with jaundice and black vomiting which occurred during 1940 in the Tagoi hills and in and around El Obeid. At the same time yellow fever was present in other parts of the province of Kordofan (East Sunad) and he points out it is suggestive that laboratory proceedures are essential for

the rapid and accurate diagnosis of yellow fever in which the isolation of the virus by inoculation into susceptible animals and the histological investigations from liver sections from fatal cases and mouse protection tests on the blood are made.

With reference to the Nuba Mountain epidemic, the attempt to isolate the virus was not commenced until the epidemic was dying out rapidly so that difficulty was experienced in finding patients in the early stages of the disease.

However, (Mahaffy, Hughes, Smithburn and Kirk) were able to isolate from patients who had experienced a mild attack of the disease, two strains of virus, and the results of studies of the reactions in animals, their immunological properties and the lesions induced by them permitted a conclusive identification of them as strains of yellow fever virus. While yellow fever virus had previously been isolated in West Africa it had not been in Central or East Africa, although the existence of the disease in the latter areas had been indicated previously by the results of immunity surveys.

The League of Nations report that in the Nuba Mountains *Aëdes aegypti* is prevalent in small numbers during the rainy season but its comparative absence in most parts of the year has led to the suspicion that this outbreak may have been due to the jungle type of the disease. Other species of *Aëdes* and *Mansonia Africana* which are known to be efficient transmitters were collected in Aircraft at the aerodromes of the Sudan.

In regard to the yellow fever situation in the Americas, Sawyer (1942) emphasizes that the outstanding characteristics of the historic yellow fever picture were sudden epidemic extensions of the disease far beyond known endemic foci, followed by the absence of the disease or relative quiescence. In his discussion of the outstanding features of the yellow fever situation in the Americas at the present time he points out

(1) Absence of definite outbreaks of urban, aegypti-transmitted yellow fever anywhere, (2) Absence of recognized yellow fever of any transmission type outside of South America, (3) Jungle yellow fever, endemic and as *migrating* epidemics in wide areas of the interior of South America, (4) Effective methods for keeping cities non-infectible through *Aëdes aegypti* control, and 5) A safe and effective way to immunize against yellow fever and prevent its spread from the jungle to infectible cities.

A report from the Brazilian Federal Public Health Service of 1942 has pointed out that *urban* yellow fever disappeared from the country and has not been present since 1934. In regard to the situation concerning jungle yellow fever "whereas 217 cases of the disease were discovered in 1937, 263 in 1938, 130 in 1939, 172 in 1940 and 19 in 1941, only 10 cases have been reported during the current year up to July 31. Since 1937 well over 2 million people have been immunized against the disease with vaccine prepared at the Rockefeller Laboratory of this city."

With reference to prevention, Sawyer points out the importance of control work carried out in American cities and that such control by keeping the city of Rio de Janeiro non-infectible, possibly prevented a serious epidemic of yellow fever in 1938 following the entrance into that city of four persons infected in the jungle areas.

Soper (1942) under whose direction the control methods have been prosecuted, points out that these include the weekly investigation of premises for *A. aëgypti* larvae, "the destruction of breeding places, and the search for additional mosquitoes by special squads, with finding and destruction of breeding foci if mosquitoes are found; the application of petroleum (3 parts fuel oil and 1 of kerosene) is recommended as being more effective than merely emptying out the water. Breeding has been so greatly reduced by such methods that in many cities it has been possible

to lower the cost of the service by lengthening the period between house inspections."

Soper also emphasizes the success that has been achieved in certain towns in South America in which there has been complete eradication of the species *Aëdes aegypti*. For example in at least six states in Brazil it can no longer be found and the same is true in certain areas in Bolivia. The success achieved in some of these campaigns, he points out, gave confidence and inspiration to the workers in the conquest of *A. gambiae* from other areas in Brazil.

Sawyer however, points out that while cities may be kept free of infection by *Aëdes aegypti* control, vaccination is the only measure practicable against jungle yellow fever and that to date it has been applied on a large scale mostly to stop an existing epidemic or to immunize against an expected one.

Bauer (1939) calls attention to the fact that during the application of the earlier type of vaccine, especially when a tissue culture virus grown in the presence of mouse embryo tissues (Lloyd, Theiler, and Ricci) and *immune* serum of either human or animal origin was used, delayed jaundice was observed among certain of those vaccinated. Attention is called by Sellards (on page 895 of this chapter) to the development of jaundice of unknown etiology in 20–30% of those vaccinated, (Soper and Smith 1938). Findlay and MacCallum had a similar experience in England in which jaundice or hepatitis developed and are inclined to believe that the jaundice was due to a contaminating virus present in the vaccine, possibly cultivated along with the virus of yellow fever in the tissue culture which had a long incubation period and a selective affinity for the liver. However, following the introduction of another strain of virus in Brazil no jaundice apparently occurred in the inoculated until 1939.

"In about 50 per cent of the individuals vaccinated with 17D virus, traces of it were found in the circulating blood after vaccination. However, it was definitely proved through a series of experiments by Whitman that this concentration is inadequate for infecting mosquitoes," and on the basis of the results of these and other experiments on both man and monkeys, Bauer feels confident that there is no danger that vaccinated persons serve as a source of infection for mosquitoes.

Fox, Penna and Para (1942) have made a careful study and give a detailed account of the icterus and hepatitis in Brazil following vaccination against yellow fever in 1939 and again in 1940. In the 1939 outbreak nearly 27% of the 304 persons vaccinated with the 17D virus became icteric for the most part during the 4th or 5th month following vaccination. In the 1940 outbreak there were 1,072 cases and 24 fatalities. From their clinical and pathological findings, which are discussed in detail, there was revealed that the disease process fundamentally involved injury to the hepatic parenchyma and there were produced in fatal cases, liver lesions similar to those seen in acute and sub-acute yellow atrophy.

Although the disease is clinically indistinguishable from the group of cases classified as "catarrhal jaundice" or "infectious" or "epidemic hepatitis," it differs from this latter group in its unusually long incubation period and in its predilection for adults. Whether the agent giving rise to the jaundice was a contaminating virus which gained entrance to the vaccine virus chain by way of human serum and persisted through an indefinite series of tissue culture passages as a strain contaminant, could not be concluded.

The outbreak which has occurred in our troops, especially between March 7th and July 4th, 1942, following the use of vaccine against yellow fever was reported by Secretary of War, Henry L. Stimpson, on July 24th when it was announced that 28,585 cases of jaundice had developed among the Army Personnel and of those effected 24,057 were among troops in the United States and 4,528 among personnel abroad. The ratio of deaths was 1 for every 461 cases, or a total of 62 deaths in all.

Circular letter Number 95, from the Surgeon General's Office, United States Army, was published in the Journal of the American Medical Association September 5, 1942, which pointed out that the peak of the incidence among the troops in the United States was reached in the week ending June 20th, since when there has been a progressive and un-interrupted decline. In this Circular there are reported epidemiological, clinical and pathological conditions regarding the outbreak. The epidemiological features have especially been studied and emphasized by Colonel S. Bayne-Jones. The pathological material has been assembled at the Army Medical Museum, Washington, D. C., and has been particularly studied by Lt. Colonel Baldwin Lucke.

The chief pathological lesions observed were those of acute or sub-acute yellow or red atrophy of the liver. Tbe earliest lesions consist of frank necrosis of liver cells in the central parts of the lobules. There are no inclusion bodies present at any stage. The lesions differ distinctly from the lesions of yellow fever. The Surgeon General, earlier in the spring, ordered discontinuation of vaccine then in use and since then the vaccine has been prepared without the human serum component and it is hoped the risk of jaundice has been eliminated.

Regulations concerning vaccination against yellow fever are matters of international importance. Those in effect for the United States Army are coordinated with British regulations applicable to areas in which yellow fever is endemic or a potential hazard. All military personnel of the United States Army, traveling to or through, or stationed in areas in which yellow fever is endemic, should be vaccinated against the disease. At the present time these endemic areas are defined as follows: "In the Eastern Hemisphere, the portion of Africa lying between latitudes 16 degrees North and 12 degrees South, including the islands immediately adjacent; in the Western Hemisphere, the mainland of South America lying between latitudes 13 degrees North and 30 degrees South, including the islands immediately adjacent, and the Republic of Panama including the Canal Zone.

"The yellow fever vaccine used in the military service consists of a special strain of living yellow fever virus which has been attenuated through cultivation in chick embryos. The material is placed in ampules and is then rapidly frozen, dessicated, sealed and stored at a temperature not higher than 0°C.

Precautions.—(1) *The vaccinating dose is* 0.5 *c.c. of the* 1:10 *dilution of the concentrated vaccine. Only one dose is required. Every precaution must be taken to avoid giving the vaccine undiluted.*

(2) After an ampule of vaccine has been opened, any vaccine which remains unused after 1 hour will be discarded.

(3) Yellow fever vaccine will be administered only to persons who are in good health and who are free from acute disease.

Reactions from Yellow Fever Vaccine.—About 5 per cent of those receiving this vaccine may exhibit a slight febrile reaction on the fifth to the seventh day."

Sellards (1941) emphasizes that effective immunization requires the injection of living modified virus and the development of an infection. In view of the severe reactions which sometimes follow the use of living

neurotropic virus from mice, he made experiments, using very dilute suspension of the French neurotropic strain injected intracerebrallv into monkeys.

When the dilution reached 1:5,000,000 or 1:10,000,000 the inoculation of 0.1 c.c. or less into the cisterna magna of monkeys produced no clinical symptoms but four out of five were immunized.

The inoculation of similar doses intracerebrally was usually followed by death from encephalitis. Out of two monkeys with gross trauma of the frontal lobe, inoculated subcutaneously with larger doses, one died of yellow fever and the other remained well and developed immunity. He points out that accidents of vaccination have occurred in any form of technique in which living virus is employed, and up to the present patients have shown symptoms of meningitis, encephalitis or myelitis, followed bv complete recovery without sequelae.

He believes that sero-vaccination has limited possibilities, for on some occasions many of the patients failed to develop a protective serum and a few of these persons subsequently developed yellow fever, some of the infections being fatal. He considers that "there is opportunity for improvement in any of the techniques in use at present and quite clearly they do not represent, in detail, the methods which will eventually be developed for vaccination against yellow fever." The sad illness, which recently terminated in death, prevented Doctor Sellards from further investigations upon this disease.

Soper (1942) with reference to the therapy of yellow fever states that the situation can be given in the words of Lin's, "the disease cures itself or kills in spite of any and every treatment." Once yellow fever has declared itself, there are no known specific serological or chemical agents of value, although there are certain clear indications for symptomatic treatment, and careful nursing is essential. (R.P.S.)

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Chapter XXIV

DENGUE AND DENGUE-LIKE FEVERS

Definition and Synonyms

Synonyms.—Dandy fever (the word "dengue" is supposed to be derived from the Spanish equivalent of dandy, or *denguero*), break-bone fever, bouquet. German: dengue-fieber.

Definition.—Dengue is an acute infectious disease due to a filterable virus transmitted by species of mosquitoes of the genus *Aëdes.*

It is characterized by an initial three or four-day febrile paroxysm of very sudden onset, a remission, which comes on about the fourth day and a terminal rise of temperature for two or three days—*the saddle-back temperature course.* Backache and pains about the muscular attachments at the joints and especially a marked postorbital soreness are important features. An eruption appears about the third or fourth day. Leukopenia and polymorphonuclear reduction are constantly noted. Apathy and a mild neurasthenic state may continue into convalescence.

The striking eruption which appears about the time of the remission of the fever has caused the term "bouquet" to be applied to it, while the severe pains in the back, joints and posterior orbital muscles suggest the name of "break-bone fever."

History and Geographical Distribution

History.—While Hirsch gives the credit for the first mention of the disease to the chronicler Gaberti, who described a disease with certain resemblances to dengue as existing in Cairo in 1779, yet, for the reason that certain clinical features of this epidemic would hardly appear to belong to dengue, as we know it, there would seem to be good ground upon which to give the credit of priority to Benjamin Rush, who, under the designation break-bone fever, gave us a true picture of dengue as it manifested itself in Philadelphia in 1780.

Gaberti was particularly impressed with the knee involvement, so that from his description the disease was known as the disease of the knees. He further noted swelling of the fingers and that the pains continued for more than a month. The sudden onset and the sweating would seem to belong to relapsing fever as well as to dengue and in support of the view that the disease described by Gaberti might have been relapsing fever we have the statement of Sandwith that bone pain, chiefly of the knee, is the symptom most complained of by the Egyptian native with relapsing fever.

Beylon, who reported an outbreak of an epidemic disease in Batavia in 1780 stated that everybody was attacked and that the symptoms were almost the same as those ushering in plague—headache, lassitude and pains in the joints. He noted, however, that this epidemic had no bad consequences, patients getting rid of it in three days under moderate diet and copious beverages. Ashburn and Craig, in 1907, proved that the disease could be transmitted by injections of blood, filtered as well as unfiltered. Bancroft (1906) and Cleland and his associates (1916) demonstrated the disease is transmitted by the mosquito *Aëdes aegypti*.

Geographical Distribution.—Dengue fever may occur in epidemic form in almost any part of the tropical or subtropical world. It is very common in the countries about the China Sea, the Pacific Islands and in the West Indies. In South America it has been reported as far south as Sao Paulo, Brazil. In Australia, in 1921 almost half of the population of Brisbane suffered from it, the infections occurring rapidly in the course of a few weeks. It is still very prevalent in North Australia and occurs along the northern and eastern seaboards, especially in the northern territory, along the central Queensland coast and the Northern Rivers district of New South Wales. In 1928, very large epidemics occurred in Greece and Egypt which attracted great attention among medical men in different parts of the world. In the years 1927–28, a million and a half people were said to have been attacked. In Cairo, in 1937, Wakil reported an epidemic of 2594 cases.

In the United States, since 1824, when the disease appeared in Charleston, S. C., epidemics have occurred from time to time which have been usually limited to the Gulf states, though sometimes the disease has occurred as far north as Philadelphia, New York and Boston. During the summer of 1885, three-quarters of the population of western Texas were reported as suffering from dengue, and in 1897 half of the inhabitants of Dallas. In 1922, and again in 1934, epidemics occurred in the southern states, when in 1922 more than a million cases were reported.

In earlier years several epidemics of the disease occurred in Honolulu, notably in 1903 when some 30,000 cases were reported. A smaller outbreak occurred in 1912. In 1943 a new outbreak started in July in Waikiki. By September the epidemic reached its peak with 160 new cases per week. The total number of cases up to the end of December, 1943, had reached 1,340 as reported by Usinger.

Sapero (personal communication, 1944) reports that dengue has appeared in epidemic proportions in many of the Pacific islands during the present World War. These epidemics have coincided with the distribution of *Aedes aegypti*. The disease spread to newly occupied islands from such old endemic foci as Tulagi, New Caledonia and Fiji. The spread through the Pacific islands began at Tulagi and continued eastward to the Hawaiian Islands where, for the first time in some years, dengue appeared in epidemic proportions in Honolulu. All occupied islands were not involved. Only those islands became affected in which *Aedes aegypti* existed before occupation and in which conditions became favorable for their increased density.

Carson (1944) emphasizes that the disease has become an important cause of absence from duty in the South Pacific combat area. The infection has been introduced into islands, where it was not present, by aviation personnel coming from infected regions. The suggestion is made that possibly *Aedes variegatus* var. *hebrideus* might be a vector although positive proof is lacking. This mosquito lays eggs in holes anywhere along the trunks of trees and the heavy rainfall provides sufficient moisture for larval development. At least two weeks absence from strenous duty was usual in the average case.

McCarthy and Brent (1943) have given an account of an outbreak in Europeans and Africans occurring in the Comoro Islands east of Tropical East Africa. The outbreaks followed a rapid increase in *Aedes* mosquitoes.

Etiology and Epidemiology

Etiology.—The disease is caused by a filtrable virus which is present in the patient's blood from the onset to the third day. No visible organism is recognized as the cause of the disease. Graham reported a piroplasm-like organism as the cause, but other workers have failed to confirm this. Couvey reported the presence of short spirochaetes in the blood 2 or 3 hours before the onset of the fever,—never later. They had

2 or 3 turns and fine extremities. Several other reports of the presence of spirochaetes in the blood have been made. However, it is now recognized that the disease occurs entirely independently of any visible microorganism. Cleland and many others have inoculated guinea pigs and rabbits without result and have been unable to find spirochaetes.

Ashburn and Craig (1907) demonstrated that a filtrable virus is present in the peripheral blood of patients from the day before the initial fever until the third or fourth day of the disease. They found that the filtrate was infective when inoculated either intravenously or subcutaneously into susceptible individuals.

The cultivation of the virus of sandfly fever and of dengue fever in the chorio-allantoic membrane of the chick embryo has been recently reported in India by Shortt. (See sand fly fever p. 918.)

Virus-containing serum remains infective for 2 or 3 months if kept in sealed tubes and in the dark. The virus is destroyed by a temperature of 50°C. for 30 minutes. However it can be dried and frozen without losing its virulence. Hoffmann and Mertens and Snijders transported the dried serum from Java to Amsterdam and inoculated volunteers with it, reproducing typical fever 285 days after the serum had been taken from dengue fever patients. Blanc, however, found that desiccated and refrigerated serum would remain virulent only 95 days. It has been found possible to transmit the virus to certain non-immune monkeys, producing after 5 days of clinically negative infection an infecting serum which will cause the disease in man, through transmission by *Aedes* that had fed on the monkey's blood. Manoussakis has shown that dengue virus can be transmitted almost indefinitely from one volunteer to another by the inoculation of the blood; in each case the incubation period being 5 to 7 days.

Transmission.—Graham, in Syria, suggested that the disease is transmitted by a mosquito, *Culex fatigans*, but no satisfactory experiments were published. In 1907, Ashburn and Craig showed that this mosquito may sometimes transmit the disease mechanically. In 1906 Bancroft, in Australia, transmitted the infection through *Aëdes aegypti*, and in a series of carefully carried out experiments Cleland, Bradley and McDonald, in Australia (1916), and Siler, Hall and Hitchens (1926) in the Philippines, demonstrated conclusively that the disease is conveyed by *Aëdes aegypti* (see Fig. 200) and not by *Culex fatigans*. It was shown that the blood of a patient with dengue fever can infect a mosquito during the last day of the incubation period and several hours before the onset of the fever and that the blood remains infective during the first 3 days of the disease. After ingesting infected blood, from 8 to 11 days (depending on the temperature) must elapse before the mosquito can transmit the infection to man, thus paralleling in a way the transmission of yellow fever. The mosquito, after it is infected, remains so throughout its life. In one instance, it is reported a mosquito transmitted dengue that was infected 75 days previously. No evidence has been produced demonstrating that the virus is hereditarily transmitted in the mosquito. When the temperature is below 18°C., mosquitoes do not become infected.

Simmons and his coworkers (1931) in Manila, showed that the dengue virus as it exists in the mosquito, *Aëdes aegypti*, is filtrable. They were unable, however, to infect larvae by adding the virus to the water in which they were reared. Apparently the virus is distributed throughout the tissues of the mosquito.

Kokzumi (1917) reported 2 positive cases in which the transmitting insect was *Aëdes albopictus* (*Stegomyia scutellaris*), and another common oriental house mosquito, (*Despoydea obturbans.*) Simmons (1940) states there was some question in these cases as to whether the precautions

taken had eliminated the possibility of natural infection with *Aëdes aegypti*. However, *A. albopictus* was reported by Morishita (1925) to transmit the disease in Formosa, and Simmons (1930) found it to be an effective vector in the Philippines. Also, in Sumatra, Schüffner and Snijders (1931) have demonstrated this fact. However, Mertens, found that in Java *A. aegypti* is a better carrier of the disease than *Aëdes albopictus*. In Florida, it has been suggested on epidemiological grounds that *Aëdes taeniorhynchus* may act as a transmitter.*

Many attempts have been made to produce infection with the virus of dengue in laboratory animals. These have in almost all instances failed. However, Simmons (1931) found that it was possible to infect certain monkeys, *Macacus philippensis*, caught at elevations above 4000 ft. in the dengue-free mountains of Luzon, and monkeys, *M. fuscatus*, imported from Japan. The disease was transmitted by *Aëdes* mosquitoes, from infected human volunteers to the monkeys, and from these animals it was transmitted through mosquitoes to other monkeys, and back to man. However, the symptoms produced in the monkeys were not sufficiently characteristic for diagnosis. Blanc (1929) also has reported the production of symptomless infections in Asiatic and African monkeys by blood inoculations.

Epidemiology.—Only dengue and influenza seem to afflict communities with such dramatic suddenness and extent. In the history of dengue there are similar pandemic recurrences as in influenza. It is not infrequent for more than half the population of a city rapidly to become victims of this temporarily most incapacitating but least fatal of the epidemic diseases. It is now believed that dengue is not transmitted in nature by *Culex fatigans*, the common culicine species of the tropics, but by *Aëdes aegypti*, the transmitting agent of yellow fever. However, as noted, Simmons (1940) and others have shown that *Aëdes albopictus* is a biological vector. Also, in some experiments in which large numbers of *Culex fatigans* were employed, it appeared that mechanical transmission of the virus might occur.

Aëdes mosquitoes are often termed the domesticated ones, since they are observed to breed and pass their lives in the immediate environment of man and further to be distinctly urban, rather than rural, in their distribution. For their breeding places they choose artificial collections of water, such as cisterns, barrels, pails, bottles and cans, in or near dwellings. These mosquitoes are small in size, silver-striped, vicious feeders, and very alert. The female alone bites, blood apparently being necessary for ovulation. It feeds especially during the morning and afternoon hours,—much less commonly at night, unless there is a light. Other points regarding this mosquito have been discussed more fully under yellow fever, Chap. XXIII.

The epidemiology of dengue fever appears to be especially dependent upon the conditions which are favorable to the development of the mosquito, *Aëdes aegypti* In its pandemic form, it not only occurs in coastal towns but may ascend mountains to an altitude of 5000 ft. When it

* Recent work tried out in the Southwest Pacific by David Atherton and others has demonstrated that *Aëdes scutellaris* is capable of transmitting the disease in experiments in human beings.

extends beyond ordinary tropical limits, the extension occurs only during the summer months or hottest part of the year, sometimes in the early autumn. In the Far East, the disease occurs particularly after the rainy season; June, July and August. It is usually more prevalent in coastal towns and about the deltas of great rivers.

Blanc (1932) notes that for an epidemic to occur the locality should have been free from outbreaks for a considerable period and that *Aëdes* mosquitoes should abound. A less dramatic outbreak is followed by the explosive one, the virus being maintained in the interval chiefly in the mosquito. At the time of its most active breeding, the widespread epidemic appears.

Pathology

As death occurs very seldom in the uncomplicated disease, reports of autopsies upon dengue fever patients have been few. Manson-Bahr (1940) notes that in the autopsies reported, localized pulmonary and intracranial inflammation were the special features. Serous effusions in the neighborhood of joints have also been noted. Myocarditis and nephritic lesions and a true encephalitis have also been mentioned. Meekins (1936) observed cloudy swelling of the viscera, particularly of the liver, which might be fatty, and a few petechial haemorrhages in the gastro-intestinal tract. Heiser (1937) mentions one autopsy in an uncomplicated case in which the only abnormality noted was an enlargement of the internal lymph nodes. There was no increase in the size of the liver or spleen.

A number of deaths were reported during the Grecian epidemic but these occurred only among the very aged and hence the lesions reported have little significance. It seems obvious that we have no definite knowledge of any characteristic pathological changes in the disease.

Immunity.—The question of immunity in dengue fever is not entirely clear. One attack frequently appears to protect. However, de Langen (1936) points out that it is certainly not exceptional to find a person having had more than one attack in an epidemic, and Manson-Bahr (1940) states second and even third attacks have been recorded. Nevertheless a number of workers have failed to reproduce the disease by injecting virus into individuals within 1 to 10 months after they have recovered from an experimental infection. Thus Schule found that certain of his volunteer American soldiers proved remarkably resistant to experimental infection with dengue blood. They had for some time been resident in an epidemic area of the disease and it was suggested that this immunity might be due to previous mild attacks of the fever.

Manson-Bahr (1940) says that immunity in dengue does not last more than six months. However, Simmons (1931) demonstrated from experiments on about 100 soldiers that a protective immunity after inoculation could last at least 13 months.

Simmons has found an immunity among natives and monkeys in endemic areas. He suggests that a virus reservoir might be maintained

in an endemic area in the absence of susceptible human beings, as has been later suggested to be the case with jungle yellow fever.

Specific antibodies undoubtedly are produced in dengue fever, as the work of Shortt (1938) in India, would indicate. Manoussakis (1928) however, observed that convalescent serum collected during the first month after recovery and inoculated into volunteers before and after the injection of virus failed to protect against infection. Other observers have obtained negative results in the few attempts which have been made to treat dengue fever with such sera.

Relationship to Yellow Fever.—There are certain resemblances between dengue and yellow fever, especially the manner of transmission and that each is due to a filterable virus; also the length of the incubation period and the type of fever are similar. Here the resemblance appears to end, as the virulence of the infective viruses is entirely different and the immunity to yellow fever is persistent for long periods. Nevertheless, many authors have stressed the similarity of dengue and yellow fever clinically and epidemiologically, and there has arisen an idea that an attack of dengue might give a certain degree of immunity to yellow fever. It is generally accepted that the immunity following yellow fever is absolute and fairly permanent, while that from dengue is most variable and individual. It has been suggested that this may indicate there are several strains of dengue virus but only a single strain of yellow fever virus. Dinger tried to infect mice with dengue virus by Theiler's intracerebral method of inoculation without effect. He subsequently inoculated a number of the same mice with yellow fever virus and all died of encephalitis. Schüffner and Snijders (1933) have successfully demonstrated that the viruses of yellow fever and dengue are distinct and the protective inoculation of the virus of one does not protect against the other. Snijders, Postmus and Schüffner (1934) used the sera of 20 volunteers who had been experimentally inoculated with dengue virus, and using both the Theiler test and Sawyer's modification, they were unable to demonstrate any protective influence of these sera against yellow fever virus. Blanc, in Greece, has also found that anti-yellow fever serum has no neutralizing action on dengue, and Stefanopaulo also showed by the mouse protection test that the serum from dengue convalescents has no influence on the yellow fever virus.

Symptomatology

After a period of incubation of from 4 to 15 days, more generally from 5 to 9 days, the disease manifests itself with striking suddenness, in fact the patient can generally recall almost the hour of the onset. The temperature rapidly rises and in a few hours reaches a maximum of from 102° to 105°F. Associated with this primary fever there is frequently a blotchy congestion of the face—the so-called initial rash.

There is usually intense headache, principally supraorbital and postorbital. The pulse rate is slightly accelerated at first, but soon becomes slow and may fall to 50 from the fourth to fifth day. There is no involve-

ment of the joints, and the so-called joint pains are really pains of the muscular insertions about the joints. The backache of dengue is usually a well marked feature. Pain on motion of the eyeballs is a prominent symptom—it is a deep soreness.

Insomnia, characterized by frequent dropping off to sleep to be awakened immediately by disturbing dreams, is often noted. The depression, mental and physical, is altogether out of proportion to the lack of seriousness of the disease. Malaise and anorexia are marked. Constipation is the rule at first.

About the third or fourth day, the temperature drops to normal or about that and remains so lowered for from 12 hours to 3 days. At this time the patient feels much better and views his affection in a less serious light. After this variable intermission, the temperature rises to

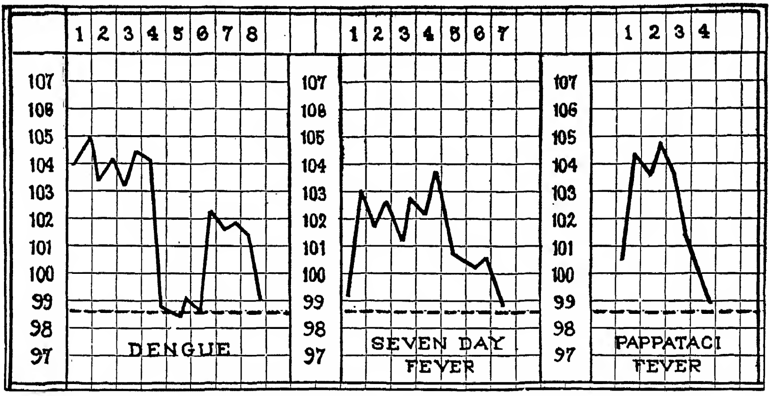

FIG. 204.—Temperature charts of dengue and dengue-like fevers.

possibly a greater height than primarily, although as a rule it is less marked. This interval, or intermission, separating two periods of fever, gives a temperature chart designated as "saddle-back." However, there may be only one rise of fever. This second febrile attack is attended with pains and possibly greater depression than the first accession. It is usually, however, of shorter duration and during this period the terminal rash appears. This is the most characteristic feature of the disease. It generally manifests itself about the dorsal surface of hands and feet, advancing up the forearms and legs. Later on it may involve all the extremities, face and trunk. The eruption is much like that of measles, but lacks the dusky red appearance of the measles rash. It may, however, be punctiform and thus resemble the rash of scarlet fever.

With the appearance of the terminal rash, crises may occur, such as profuse sweating or marked diarrhoea or epistaxis. The desquamation is furfuraceous in character and may be attended by marked itching. In some patients (Caucasian) there is a rosy carmine flush of the palms of the hands and soles of the feet. Some authorities have reported glandular enlargements in dengue.

Leukopenia and polymorphonuclear percentage reduction appear by the second day.

CLINICAL CHART

ONE HUNDRED CASES OF DENGUE FEVER

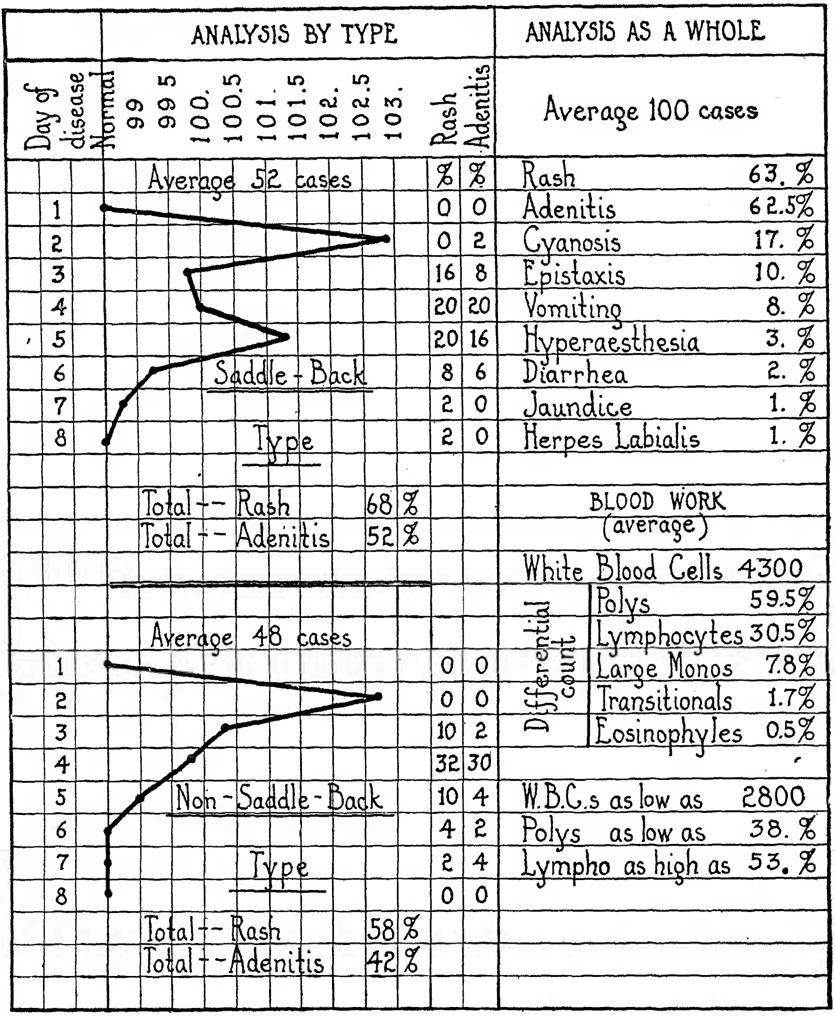

FIG. 205.—Dengue. Analysis of Symptoms, from 100 cases occurring in an epidemic at St. Thomas, V. I. (After Lane, from U. S. Naval Medical Bulletin.)

Convalescence is apt to be protracted, being especially characterized by malaise and nervous depression, and sometimes neurasthenia.

Clinical Types.—In different epidemics it is noted that some one clinical feature may seem outstanding. Of these we may note:—

(1) The pulse rate is slow for the temperature rise, thus reproducing a phenomenon common in yellow fever (Fagèt's sign). It is in recent epidemics particularly that clinical descriptions have recorded the frequency of a very slow pulse, most of the older authorities having noted a pulse rate which corresponded to the elevation of temperature.

(2) In some epidemics the feature of glandular swelling is prominent, while in others the swelling is so slight as to be overlooked.

(3) The characteristic "saddle-back" temperature chart seems lacking in the majority of the cases in certain outbreaks. It is possible that some such epidemics, showing atypical temperature curves, may have been due to phlebotomus fever, an allied virus, or seven-day fever, instead of dengue. However the temperature is often variable as regards type in the same outbreak.

(4) In some epidemics, the rash is insignificant or very slight in most cases. This observation is possibly dependent on the ephemeral character of the eruption in certain groups of cases.

(5) From the chart Fig. 205, analyzing the symptoms in one epidemic, it will be noted that Lane observed cold, clammy, dusky extremities in 17 per cent of his cases. This is an unusual finding.

In the Athens epidemic, gastro-intestinal disturbances, vomiting, epigastric pain, and haemorrhages into the skin and mucous membrane, together with complications such as parotitis, otitis media, and bronchopneumonia were noted. De Langen (1936) has noted as complications febrile albuminuria, parotitis and orchitis.

Symptoms in Detail

Onset and the Temperature Chart.—Dengue probably sets in more abruptly than any other disease. The temperature chart is often typically saddle-back.

The Pains.—Very marked soreness is often experienced deeply seated about the place of origin of the ocular muscles, so that every movement of the eyeballs is at once complained of as giving pain.

General pains all over the body are common, more especially of the back and about the tendinous insertions of the muscles, which cause the pains to be referred to the joints. The knee-joint pains are probably the most frequent. The rachialgia may be as great as that in variola or yellow fever.

The Eruption.—The characteristic eruption does not appear until about the time of the intermission, or with the accession of the terminal fever. The fall of fever about the third or fourth day is often attended by a critical epistaxis, sweat, or diarrhoea, to be succeeded by an intermission of from 1 to 3 days of a feeling of well-being. About this time, or with the secondary rise of fever, the true dengue rash appears. It is at first noted frequently about the bases of the thumbs and extending over the dorsal surfaces of the wrists. Almost simultaneously a measles-like rash appears over the dorsal and internal surfaces of the big toe, extending to the ankle, especially over the internal malleolus. Later on the elbows

and knees may be involved, or the rash may cover thickly the entire body. A carmine flush of the palms of the hands and soles of the feet is not uncommon. A furfuraceous desquamation, with much itching, at times follows the eruption. The so-called primary eruption is nothing more than an initial flushing of the face; it is ephemeral. The true dengue rash may also be quite ephemeral, but usually it lasts for 2 or 3 days, or rarely 4 or 5 days.

The Nervous System.—Besides the headaches, insomnia and depression are common and may extend through convalescence. Apathy is marked.

The Blood.—The disease produces little or no change in the erythrocytes or haemoglobin, but one of the most constant features of the disease is a marked leukopenia, which was emphasized by Stitt (1906). Reports, however, do not entirely agree as to the duration and degree of the leukopenia, or as to the type of cells involved. Stitt frequently observed a leukopenia of about 4000 from shortly after the onset, with a reduction of the polymorphonuclears to about 45 per cent. During the attack, the eosinophiles are decreased, but there is an increase during convalescence. Simmons, in an experimental inoculation of 80 cases of dengue in white American soldiers in Manilla, found that all developed leukopenia, that the leukopenia usually began by the second day and progressed to a low point of about 2000 cells on the fourth or fifth day after onset. The counts returned to normal levels several days later than did the temperature. The leukopenia was produced by a decrease in both the mononuclear and the mature neutrophilic polymorphonuclear cells. The latter showed marked degenerative changes during the fever and decreased numerically from a normal of about 3000 cells to levels as low as 300 cells. Coincident with this decrease in the mature cells, there was a marked increase in the immature granulocytes, which often began on the day preceding the initial fever and lasted throughout the infection. This early "shift to the left" he found was a constant reaction which often made it possible to anticipate the onset of the disease in the experimental infections.

Mortality.—Very few deaths have been reported, except among infants and aged persons, when the condition has generally been complicated.

Sharp and Hollar (1935) record one death per 1000 cases reported by Robertson (1905) in an epidemic at Brisbane, and one death per 5000 reported by Schrumpf-Pierron at Cairo in 1929. In 1928, in an outbreak in Greece, the death rate reported by Pontano was 1 per cent, while Cardamitis gave the mortality rate as 1 to 61,000. Griffiths and Hanson state that in the records of the City of Athens, Greece, for August 1928, 32.6 per cent of the deaths were certified as due to dengue. In Piraeus, where it was estimated that 90 per cent of the population became infected, 39.7 per cent of the deaths were reported as caused by dengue. However, during this enormous epidemic it seems likely that some other virus infection was likewise present and influenced this very high and abnormal death rate for dengue fever. Wakil and Hilmy (1938) reported

in the epidemic in Cairo of 2594 cases that 50 deaths occurred from pulmonary and cardiac complications.

Diagnosis

No definite laboratory test has been developed for the identification of the dengue virus, and the specific diagnosis rests largely upon the clinical observations and examination of the blood.

The two diseases with which dengue can be most easily confused are influenza and yellow fever. In fact, when the great pandemic of influenza (1890) first made its appearance in France, many regarded it as an atypical form of dengue.

The respiratory involvement of influenza, and the eruption and comparatively slow pulse of dengue are the principal points of difference. It must be remembered that affections in the tropics, diagnosed as influenza, have shown but slight respiratory symptoms, the cases being more of a nervous or intestinal type. The eruption of dengue may fail to appear, or be missed in the study of the case. The blood findings should aid in differentiation from influenza, as is also true of yellow fever, a disease which likewise has blood findings of practically a normal character. Other than the blood picture, we have in yellow fever (1) albuminuria, coming on about the second day, and (2) jaundice appearing about the third day. In dengue, the eruption appears from the third to the fifth day. Albuminuria is usually absent in dengue. However, febrile albuminuria is noted as a complication by de Langen (1936).

Dengue may be mistaken for measles, but the early coryza, Koplik spots and marked rash, first appearing about the face, should differentiate.

In scarlet fever, the rapid pulse, angina and leucocytosis should be sufficiently differentiating.

Confusion with articular rheumatism may arise when the pain about wrists, knees and ankles has been mistaken for true joint involvement.

The headache and backache of smallpox may be confusing until the eruption about the forehead appears. The leukopenia of dengue is the main differential point in these first 3 days of doubt.

Papataci fever and Rift Valley fever, caused by immunologically different viruses, show symptoms of the leukopenia as observed in dengue. The Seven-day fever of Rogers in India and Six-day fever of Deeks in Panama, and the Five-day fever of Van der Scheer in Batavia, may closely resemble dengue and are probably either identical with dengue, or due to closely related viruses.

Prophylaxis and Treatment

Prophylaxis.—This would seem to rest entirely upon the question of destruction of mosquitoes and prevention of the infected mosquito from biting an individual. In dengue, the virus is apparently in the blood for 3 days, so that screening of patients is necessitated for this time and for a longer period than for phlebotomus fever.

Because of the high incidence of dengue, particularly among American troops in the Philippines, attempts have been made by Army medical officers to develop a prophylactic vaccine. No protection, however, has been demonstrated by such measures—as blood rendered non-infective by freezing, drying, and storage, and saline suspensions of macerated, infected insects rendered bacteria-free by the addition of phenol or formalin.

St. John and Holt also prepared a prophylactic against dengue by extracting the liver and spleen of dengue-infected monkeys. However, it did not protect volunteers from an experimental infection later, although some of the attacks seemed to be milder.

Treatment.—The malaise and depression are generally so great that the patient keeps his bed voluntarily. A light diet is indicated, although the anorexia is so marked that it is difficult to persuade a patient to take food. Cold spongings, provided the patient is not disturbed by being moved, are of value for the insomnia. Phenacetine or aspirin may be given for the relief of the headache, and backache. It is rarely necessary to give morphine. During convalescence, tonics are indicated, and if there is any condition where a good wine is of value it is this, to counteract the terrible depression. It has been suggested that adrenal insufficiency may account for the asthenic, protracted convalescence, and from this standpoint adrenalin has been recommended. In the Athens epidemic, urotropine was found to be of value when given in full doses in the early stages.

Dengue-like Fevers

There are a group of febrile conditions which in many respects resemble epidemic dengue fever and which occur more frequently in sporadic cases but which differ from one another in their duration rather than their symptomatology.

Van der Scheer described such a fever in Batavia, with a course of 5 days. This became known in the Dutch East Indies as the *Five-day fever of Van der Scheer.*

Deeks in Panama described a very similar condition with a course of 6 days, Rogers in Calcutta one lasting 7 days, Baermann in Delhi, Sumatra, one lasting 9 days. Others have been described in different parts of the world, varying from 3 to 10 days. In the disease described by Deeks in Panama, there was a continuous fever for 6 days and an enlargement of the spleen which was said to differentiate it from dengue.

DeLangen (1936) points out that the Five-day fever of Van der Scheer is spread widely over the entire East Indies and that it is impossible and unnecessary to differentiate all these dengue-like fevers from one another, as they all have the same symptomatology, but only differ locally in duration. Thus he points out that in the same place the attacks may be of different duration, and that in Batavia they not only have the Five-day fever of Van der Scheer but similar types lasting anywhere from 2 to 10 days. The virus is transmitted by the same mosquitoes and is filtrable. Moreover, Snijders and Binger fed mosquitoes, *Aëdes aegypti* and

A. albopictus, on endemic cases of dengue in Medan, Sumatra, and then sent them to the Colonial Institute in Amsterdam, where they were re-fed on volunteers where fever had never been previously reported. All of the volunteers subsequently developed dengue, but it was shown that the same virus in the same batch of mosquitoes produced different types of fever in different individuals. In one case it showed a typical saddle-back temperature, in another a continuous fever lasting 7 days. From this it appeared that the Five-day fever of Van der Scheer and the Seven-day fever of Rogers are not distinct diseases.

There has also been described a condition called the red fever of the Congo, which was formerly thought to be a form of yellow fever. Findlay has more recently emphasized that it much more resembles dengue than yellow fever.

It should be borne in mind that there is a form of leptospirosis which has been encountered in Japan which is caused by *Leptospira hebdomadis*. Its differentiation from dengue was made possible by the discovery of *Leptospira* in 1918 by Ido, Ito and Wani.

Rift Valley Fever (Enzootic hepatitis) is an epizootic disease of sheep, caused by a filtrable virus described by Daubney, Hudson and Garnham in 1931. During the study of a severe epidemic in Kenya, British East Africa, it was noted that the native shepherds, and later Europeans, in contact with the affected animals developed a short illness resembling dengue. These investigators also produced the disease in a volunteer by inoculation with the blood of an infected sheep. Since that time a number of laboratory workers in this country and abroad have contracted the disease while studying the virus.

The disease can be transmitted to cattle (a small epizootic of natural infection is recorded), goats, certain species of monkeys, rats, mice and other small rodents. Guinea pigs and rabbits, however, appear to be resistant. The infection can be produced by application of the virus to scarified skin, the conjunctivae, or nasal mucosa, as well as by subcutaneous or intraperitoneal injection. There is some evidence to suggest that mosquitoes of the genus *Mansonia* act as vectors, but this has not been definitely proved. The characteristic pathological lesion in lambs, and also in inoculated mice, is a marked focal necrosis of the liver. Stained sections show acidophilic intranuclear inclusions in the hepatic cells.

Mackenzie and Findlay (1936) obtained a "fixed" neurotropic strain of Rift Valley fever virus by the injection of immune serum into an animal prior to an intracerebral inoculation of virus. Some of the nerve cells showed intranuclear inclusions similar to those produced by the neurotropic type of yellow fever virus. They suggest that this restraining action of specific antibodies may produce neurotropic variants of other viruses, and that the occurrence of nervous sequelae in virus infections in man may be explained in a similar way. The *virus* occurs in the blood, liver, spleen and other organs early in the disease in both animals and man. It will pass through Berkefeld candles N, V, and W; and Broom and Findlay have estimated its size at from 23 to 35 $\mu\mu$ by filtration through collodion membranes. Mackenzie has cultivated the virus in a medium of chick embryo and Tyrode's solution. It can be preserved in blood containing 0.5% phenol for months in the ice chest.

Immunity.—The serum of convalescent animals and man contains virus-neutralizing antibodies for several months after recovery, but the immunity is not permanent. Broom and Findlay have demonstrated complement-fixing antibodies which are apparently specific for Rift Valley fever, and which they found to persist for at least 6 months.

Francis and Magill (1935) have shown that the inoculation of insusceptible animals such as the rabbit also results in the development of virus-neutralizing antibodies.

Marschall (1942) has compared the histological changes of the liver in mice and hamsters infected with Rift Valley Fever virus with those seen in Yellow Fever. He finds that there are striking similarities, in that the Councilman bodies resulting from scattered necrosis may dominate the picture in both infections and the intra-nuclear inclusions are also similar. However, he points out that there is little danger in the diagnosis of Yellow Fever being complicated during the examination of human specimens of liver obtained by viscerotome. He points out that Rift Valley Fever produces only a mild infection in man.

The *diagnosis* of Rift Valley fever depends upon the demonstration of the virus in the blood by mouse inoculation in early cases, or of virus-neutralizing antibodies later in the disease. The clinical picture resembles that of influenza, dengue, or yellow fever. The virus of influenza, however, is not present in the blood; and the viruses of dengue and yellow fever are not pathogenic for mice on intraperitoneal inoculation. There is no cross immunity with the viruses of dengue or yellow fever.

Bwamba Fever.—Smithburn, Mahaffy and Paul (1941) have encountered in Uganda a fever which they believe is a clinical entity. They report that the disease is characterized by rather sudden onset, fever, headache, and backache. The symptoms persist for about 5 to 7 days and subside without sequelae. They have not observed fatal cases. Nine strains of a filtrable virus were isolated from the blood of 9 patients suffering with the disease. The original sera of the patients failed to neutralize the virus whereas convalescent sera contained neutralizing antibody against it. The virus was pathogenic for and caused death of mice by intracerebral or intranasal inoculation. It caused non-fatal febrile illness when given intracerebrally to rhesus monkeys. Guinea pigs and rabbits were not susceptible. The lesions caused by the virus in mice were essentially limited to the nervous system and were characterized by damage to the cortical cells and by the appearance of intranuclear acidophilic bodies resembling inclusion bodies.

Phlebotomus or Pappataci Fever, Sandfly Fever, Three-day Fever.—Phlebotomus fever was first described in Dalmatia. Later it was proved to be very widely distributed. It was shortly afterwards observed in the Balkans, Italy, Portugal and all the countries bordering on the Mediterranean. It also occurs in British India, China, East Africa and South America. Recently an outbreak occurred in northern Argentina. Its range appears related to the distribution of the sand fly, *Phlebotomus*.

Manson-Bahr points out that where *Phlebotomus* is absent, as in Bermuda, the fever is not found. Delangen and Lichtenstein (1936) state that it is not present in northern India. During the Great War it was prevalent in Gallipoli, Salonica, the Agean Islands, Egypt, Palestine, Syria, Iraq, and India. In India, it has been encountered up to a height of 4000 ft. In the Western hemisphere, it has recently been reported in northern Argentina.

Etiology.—This disease, which is often called three-day fever on account of its running its course in this period, is caused by a filtrable virus (Doerr, 1908). This virus only seems to be in the blood of the patient's peripheral circulation during the first 24 hours of the illness. Blood abstracted after the end of the second day and injected into a well person fails to reproduce the disease. If the blood is filtered through a Pasteur candle F, the filtrate will set up an attack just as well as the unfiltered blood, in this respect being like dengue and yellow fever.

Shortt, Rao and Swaminath (1936) reported the cultivation of the virus of sandfly fever upon the chorio-allantoic membrane of embryo chicks, and Shortt, Pandit and Rao (1938–39) have confirmed this cultivation. They consider that the proof of cultivation of the sandfly

fever virus in the chorio-allantoic membrane depended not only upon the production of focal lesions in the egg but because the serum of patients convalescent from sandfly fever was able to neutralize the lesion-producing agent in the material. Of 6 convalescent sera tested, all but one inhibited growth of the virus on the membrane. The controls with normal human serum all showed growth of the virus, while the convalescent sera by themselves gave no growth. By infiltration experiments, through graduated membranes, the size of the virus was determined to be about 160$\mu\mu$ in diameter.

Anderson (1941) has attempted to diagnose Sandfly fever by making cultures of the virus in the chick embryos by the technique described above by Shortt. Samples of the blood of 132 patients suspected of having Sandfly fever were examined. Positive cultures or results were obtained in 78; doubtful in 14 and negative in 40. Obviously little importance can be attached to negative results.

Transmission.—The transmitting agent is a sandfly or moth midge, *Phlebotomus papatasii.* This midge, as is true of the psychodid family to which it belongs, is very hairy. It has long slender legs and narrow wings. The proboscis is as long as the head, and the lancets project beyond the labium.

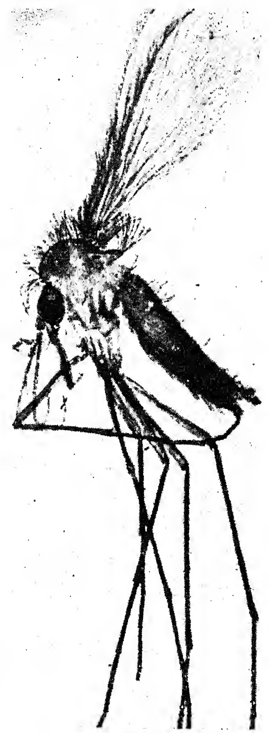

FIG. 206.—*Phlebotomus papatasi* female. (After Doerr et. al.)

The female alone bites, which act takes place chiefly at night; cool, moist, shady places, away from sleeping rooms, being preferred by the insects in the daytime. The insect is a persistent, vicious feeder, difficult to escape from as, owing to its slender size, mosquito nets usually employed offer no protection. It takes from 6 to 8 days after feeding on a patient in the first day of the fever before the midge is capable of transmitting the disease. Doerr thinks that the papataci virus may be transmitted hereditarily by the insect to the egg. Whittingham and Rook confirm the transmission from generation to generation.

At present, of the genera of the 3 families of midges, only *Phlebotomus* is known to transmit disease. *P. papatasii* transmits phlebotomus fever in the Balkans. *P. minutus* has been reported as the host at Aden. Another species, *P. perniciosus* is also said to transmit the disease. However, there has been much confusion in the differentiation of the species and some entomologists believe that *P. papatasii* is the species commonly concerned in transmission.

These moth midges are 2 mm. in length and have the body densely covered with long yellow hairs. The second longitudinal vein has three distinct branches. The antennae have 16 restricted joints and the proboscis is as long as the head. The species of *Phlebotomus* are separated by slight variations in wing venation, palpal lengths, etc.; thus the second segment of palpi of *P. papatasii* is a little longer than the third one, while with *P. perniciosus* these segments are of equal lengths. In *P. minutus* the second segment is only half the length of the third. The insect lays about 40 eggs in damp dark places. The period of metamorphosis from egg to insect is about one or two months, according to temperature.

Phlebotomus larvae die out in dry soil and very wet earth is unfavorable. Moderate moisture and protection from light seem necessary for their development. The remains of dead insects also seem to make good breeding places. It is in cracks of old damp brick or stone walls that the female most often deposits her eggs. Caves are also selected. As the favored breeding places are cracks in walls, or the ground surrounding buildings, these should be filled in and made inaccessible to the midge. If breeding is thus prevented 200 to 300 feet from the house it keeps the female *Phlebotomus* from getting a blood feeding on account of the distance.

Blood seems necessary for the fertilization of the eggs but lizard blood seems more common in the stomach of *P. minutus* than human blood. They have also been observed to feed on other reptilian bloods. The female insect has been kept alive in captivity up to forty-six days.

Cases of phlebotomus fever first appear in the late spring and the disease becomes epidemic during the summer. An attack produces a marked immunity. The disease has chiefly been studied in the Balkan States but undoubtedly it is widespread. It is almost never fatal so that we know nothing of its pathology.

Symptomatology.—The symptoms of phlebotomus fever answer very well for cases one sees in an epidemic of dengue fever in which instead of the saddle-back course of fever, we have a three-day primary rise and then a fall to normal without any secondary fever rise. Cases of phlebotomus fever are occasionally reported where the fever continues seven or eight days.

The symptoms as usually given are as follows: After a period of incubation of from 3 to 7 days there is an abrupt onset, with congested face and injected conjunctivae. Manson-Bahr says the conjunctivae are sometimes so injected that they have been likened to those of the mastiff. There is pain in the head, eyes and back. There is marked malaise, with great depression of spirits. There is anorexia, with coated tongue, and rarely vomiting and diarrhoea. There may be some congestion of the pharynx, and even a slight bronchitis. It may resemble influenza so closely clinically, that a synonym is "summer influenza." The liver and spleen are normal. DeLangen emphasizes that the nervous system may be most intensely attacked and may form the center of the clinical manifestations. The patients may feel very ill and be weak and apathetic and suffer from intense mental depression. Epistaxis is rather common. There is a leukopenia and polymorphonuclear percentage decrease. The two points which are chiefly advanced in its clinical differentiation from dengue are (1) slow pulse, a bradycardia, and (2) usually only 3 days of fever and absence of eruption. However, bites of the sandfly may cause a considerable amount of irritation, resulting in hyperaemia and even in oedema. Some writers have even reported not only a hyperaemia but an exanthema. However, in such cases it was noted that it appeared at no fixed period, as with dengue fever.

The dengue-like fevers of India are practically identical clinically with phlebotomus fever. The usual idea is that dengue epidemics are far more explosive in character than is true of epidemics transmitted by the sandfly. The strongest point in differentiation of sandfly fever and

dengue is that neither is said to confer any immunity for the other disease. The distinctions of enlarged glands and break-bone pains are often advanced as characteristic of dengue and not of sandfly fever. Stitt never observed other than slight glandular enlargement in dengue cases. However, in endemic dengue in the East Indies, deLangen states, general swelling of the lymph nodes may be striking.

Treatment is purely symptomatic. Aspirin has proved valuable for the relief of the headache. Morphia is rarely necessary to control the pain. The patient should be advised to rest for several days following the subsidence of the fever. Otherwise the asthenia is liable to continue for a longer period. The prognosis is entirely favorable. No serious complications are known to occur. No deaths have been known to have been caused by the infection.

Prophylaxis depends particularly upon the prevention of the bites of sandflies. Unfortunately a mosquito-net having a mesh sufficiently small to keep out sandflies is almost intolerable for use by a white man in a hot climate. Nevertheless, as the *Phlebotomus* does not *usually* fly higher than 10 ft., the removal of inmates to the upper story is usually a very effectual preventive measure. Repellants such as camphor and oil of citronella are of value in keeping away the midges. Electric fans, or currents of air, are also frequently very effective in ridding quarters of *Phlebotomus*. Attempts should be made to eradicate the breeding places of the fly, which have already been discussed.

Sellar Fever.—Jack (1937) has described an infection in the Delhi-Meerut area in India which he regards as a disease *sui generis* to which he gives the name of sellar fever. He points out that the clinical picture suggests a resemblance to the sandfly-dengue group, but there are many definite differences. However, O'Meara (1938), who has also studied this fever in the same areas, points out that the word "sellar" is "saddle," and that saddle-back fever is simply another name for dengue.

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Chapter XXV

DISEASES DUE TO RICKETTSIA

(*The Typhus Group of Fevers*)

Introduction.—Through epidemiological, pathological and immunological studies, we have been enabled to differentiate three important groups of human disease caused by rickettsiae: (1) the typhus group; (2) the Rocky Mountain spotted fever group; and (3) the Japanese river fever group. The Rickettsia of Q Fever is also distinctive. The typhus fever group includes the epidemic or louse-borne fever and the endemic, flea-borne typhus, or murine typhus, so termed on account of the natural reservoir in rats. The Japanese river fever group, also known in Japan as kedani disease or tsutsugamushi disease, embraces several more or less closely related mite-borne infections which have been encountered in Southern Asia, Japan, Formosa and Oceanica. The Rocky Mountain spotted fever group includes the forms of the disease transmitted by ticks—as Rocky Mountain spotted fever of North America (eastern and western types), Sao Paulo exanthematic typhus of Brazil, probably fievre boutonneuse of the Mediterranean countries and Northern Africa, and South African tick bite fever. Fievre boutonneuse of the Mediterranean coast is apparently caused by a strain of Rocky Mountain spotted fever virus, modified by residence in the dog and in the dog-tick. At least there may be complete cross-immunity between the organisms of these two diseases, although they are clinically different. Certain immunological reactions, however, indicate that there are minor biological differences between the two viruses and Rocky Mountain Spotted Fever vaccine does not protect against fievre boutonneuse.

Rickettsiae Pathogenic for Man.—The term *Rickettsia prowazeki* was first applied in 1916 by Rocha-Lima to the cellular inclusions observed in the intestines of lice which had fed on patients with typhus fever. He proposed this name in honor of the scientists Ricketts and Prowazek, both of whom succumbed while studying the disease.

Von Prowazek formerly thought that the Rickettsiae were probably closely related to the protozoa. Morphologically they resemble small pleomorphic bacteria. How closely they are related to bacteria is still not entirely clear but there has been much evidence which has made it appear advisable to separate them from the true bacteria on the one hand and from the filterable viruses on the other. They differ from most bacteria in being able to grow only within living cells and in this respect they are more closely related to the filterable viruses. However, they differ from many of the filterable viruses in that most of them are slightly too large to pass through fine bacteriological filters. The virus of Q Fever is the only pathogenic one known to be definitely filtrable.

The Rickettsiae are encountered in the tissues of arthropods, as well as in man and other mammals, and live and multiply only within the cytoplasm of living cells. Some writers, however, include some of the similar but extra-cellular organisms found in arthropoda as Rickettsiae. None of them have been cultivated upon the usual bacteriological media.

Morphologically the organisms are diplococcoid and show great variation in size and shape, from almost invisible particles to bodies approaching 2μ in length. Stained with Giemsa, they take a purplish tint, and with Castaneda's stain they are light blue in color. The Machiavello stain is most satisfactory. These tints are unlike those of ordinary bacteria stained by these methods. They are Gram negative. While not cultivable on ordinary media, they grow in the cells of tissue cultures. Plotz, Smadel, Anderson and Chambers (1943) have reported upon the morphological structure of rickettsiae with the aid of a type B R CA electron microscope.

Plasma clot tissue cultures were first obtained by Wolbach and Schlesinger of the Rickettsia of Rocky mountain spotted fever. Subsequently, the chorio-allantoic membrane of living chick embryo and the Maitland medium with minced chick embryo in a mixture of guinea pig or rabbit serum and Tyrode solution, proved more satisfactory media for cultivation.

It has been suggested, but not proved, that the genus *Rickettsia* was originally adapted to plants, later becoming parasites of mites feeding on plant juices, and subsequently infecting rodents on which the mites fed. From such infected rodents, lice, ticks, and fleas became of importance in rickettsial epidemiology.

Species.—The important species which have been demonstrated as pathogenic for man are as follows: (1) *R. prowazeki*, the cause of typhus fever. Two different varieties of this organism have been recognized—*R. prowazeki*, the cause of epidemic European louse-borne typhus, and *R. mooseri*, the cause of endemic, flea-borne, murine typhus; (2) *R. rickettsi* (*Dermacentroxus rickettsi*, Wolbach), the etiologic agent of Rocky Mountain spotted fever and also the name given to the infective organism of several other diseases which may be regarded as strain variants; (3) *R. orientalis* (Nagaya), *R. tsutsugamushi* (Ogata, 1931), and *R. niponica* (Sellards, 1923), the names which have been given to the etiological agent of the group of mite-borne diseases which occur in the Far East. These diseases have many features in common with those of typhus and Rocky Mountain spotted fever, but are characterized by the presence of an initial local lesion and the organisms appear to be distinct immunologically.

Q Fever.—Derrick (1937) and Burnet and Freeman (1937) have also reported a rickettsia-like organism growing inside, but also outside, of cells, as the cause of Q fever in Australia. Derrick (1938) has named the species *R. burnetti*. The bandicoot, *Isodon macrurus*, is believed to be the natural reservoir of the infection, which is probably transmitted by a tick, *Haemaphysalis humerosa*. (See also page 973.)

A similar organism has recently been found in wood ticks, *Dermacentor andersoni*, in Montana (Parker and Davis, 1938). Dyer (1938) has reported a case of probable laboratory infection with it. The disease has

been named "Nine-mile fever." Pinkerton (1940) reports that there is no cross-immunity in guinea pigs between the organism of this disease and that of typhus or of spotted fever.

More recently Cox (1940) has pointed out the close relationship of this malady to that of Q fever of Australia. Tests which he has carried out with guinea pigs have shown that American Q fever shows no cross-immunity with Rocky Mt. spotted fever, Brazilian spotted fever, boutonneuse fever, or epidemic and endemic typhus. Tests carried out by Dyer on this infectious agent, which is filter-passing and isolated from ticks, and later by Cox, have definitely shown that there is complete cross immunity with it and the organism Q fever of Australia.

Cox has suggested the name of *Rickettsia diaporica* for the organism. He has cultivated the organism in tissue culture of the developing chick embryo. The best results were obtained with flasks containing chick yolk sap tissue suspensions, in filtered human ascitic fluid. From such a source by a fractional centrifugation practically pure suspensions of *R. diaporica* suitable for agglutination tests have been secured. Sera from monkeys and rabbits recovered from American Q fever agglutinate suspensions of *R. diaporica*, but fail to show agglutinins for *Brucella abortus*, *Bact. tularense*, and the OXK, OX_2, OX_{19}, and XL strains of *Proteus*.

In infected guinea pigs, rickettsiae were found in great numbers in the inflammatory exudate of the skin and in the cellular exudate frequently found covering the spleen. They were also present in large numbers in the spleen substance and in the tunica and polar fat of the testes. They were often extracellular, but in many cases abundant intracytoplasmic forms were found. The cell nuclei were not commonly invaded, but in a number of cells in which nuclei appeared to be vacuolated, rickettsial forms were seen within the vacuoles.

Rickettsia-like Organisms.—Many rickettsia-like organisms found extracellularly in the intestine of arthropods and presumably non-pathogenic have been reported. Wolbach (1940) has listed 39 nonpathogenic rickettsial organisms in 14 species of arachnids (ticks, mites, and spiders) and in 22 species of hexapods ("insects"), including numerous non-blood-sucking insects, as well as lice, ticks and midges. Among these he lists *R. pediculi*, *R. quintana*, *R. wohlnica* of the body louse, and *R. melophagi* of the sheep's ked. These are not intracellular and he does not include them in his classification of the family "Rickettsiazeae."

Other Diseases.—There is some evidence for believing that *R. pediculi* may be the cause of trench fever. Opinions, however, differ in this connection and Zinsser (1940) states that the evidence is far from being convincing. See Chap. XXVIII (Trench Fever).

Rickettsia-like organisms have also been found by Siler and Sellards (1938) in about half of the mosquitoes, *Aëdes aegypti*, fed upon patients with dengue fever. They, however, did not suggest a definite etiologic relationship of this organism to dengue fever and such a relationship has not yet been established.

Trachoma.—Other organisms which should not be classified as Rickettsia recently have been reported as pathogenic for man. Cuenod and Natof (1937) believe that their experimental evidence shows that trachoma is caused by Rickettsia. They collected trachoma material from a patient and injected it into the testicle of a guinea pig, a culture of Rickettsia being obtained in this manner. Lice were then injected with this culture. After the culture material was passed through a series of lice, it was inoculated into the conjunctiva of an ape, which developed clinical trachoma. One experiment consisted of injecting the conjunctiva of a blind human eye with this Rickettsia culture in lice. This was followed by clinical trachoma, confirmed by laboratory and microbiologic tests. Poleff (1937) has confirmed this work in Madagascar and Thygeson has studied the virus of inclusion conjunctivitis in the United States. Foley and Parrot gave the name *R. trachomitis* to the organism apparently described as *Chlamydozoon trachomitis*, [Halberstaedter and Prowazek 1907], while Donatien and Lestogard regard it as identical with *R. conjunctivitis* Coles of ruminants (sheep and cattle). Burnett (1937) classifies this *Rickettsia* of trachoma in a separate group and states that no bodies are present in trachoma other than the well-recognized Halberstaedter-von Prowazek bodies. Donatien and Lestogard (1938) believe these bodies are the initial ones in the cycle of the organism. However, Bengston (1938) questions whether the various stages of the inclusion bodies in trachoma are rickettsial in nature.

Psittacosis.—Although a number of reports appear to have established the filterability of the infective agent of Psittacosis, Lillie (1930), Blanc and Canti (1935) give evidence for regarding psittacosis as a rickettsial disease. Laidlaw (1939) using graded colloidon membranes, gives the size of the infective virus particles as 0.25μ and Lazarus, Eddie and Meyer (1937) 0.2–0.3μ. The virus of psittacosis will pass Chamberlands L, L2, and Seitz E. K. filters. Nevertheless the dimensions of the "particles" of the virus given suggest that it is visible. Leventhal (1930), Coles (1930) and Lillie (1930) all found such bodies in the infected spleens and livers of parrots with psittacosis. From the names of their discoverers, they have become known in literature as L.C.L. bodies.

In sections stained with Giemsa's solution they appear as tiny blue spherical or ovoid cocci, or bacillary forms lying either in the cytoplasm of certain mononuclear cells or free in the tissue spaces. Rivers (1931) found small cocci or short bacillary structures 0.2–0.25μ in diameter or length. Lille has proposed the name *R. psittaci* for them. However, Bedson and Blood (1934) did not find bacillary bodies, but round bodies which might measure 1μ in the monocytic cells and which they regarded as made up of elementary bodies. It has been suggested that they are plasmoidal inclusions analogous to the Guarnieri bodies in vaccinia and not rickettsial. Enders (1940) takes this view, especially because an arthropod ("insect") vector has not been demonstrated.

Lymphogranuloma Inguinale.—Miyagawa (1935) first reported *Rickettsia* in 20 human cases of Climatic bubo (*Lymphogranuloma inguinale*),

the organisms being found mostly in histiocytes, but also sometimes in leucocytes, glia cells and lymphatic cells. The organism was cultivated upon chorio-allantoic membranes of chick embryos. The presence of these rickettsiae in this disease have been confirmed, not only by several other Japanese investigators, but recently by Nauck (1937) Mauro (1937), Findlay (1938), and others. Brumpt (1938), on account of this recent work and after examining Miyagawa's specimens, has suggested a new genus and species for this *Rickettsia—Miyagawanella lymphogranulomatosis*, nov. sp.

Mosing (1936) an assistant of Weigl and working in Weigl's laboratory, has proposed the name of *R. weigli* nov. sp. for an extracellular "*Rickettsia*" which he says is larger than *Rickettsia prowazeki* and that he found in the intestine of lice, and that produces a febrile infection in man, consisting of a fever which relapses on the third day. The Weil-Felix reaction is said to be negative.

Herzig (1939) reports that among 40 to 50 people in Weigl's laboratory upon whom lice were fed for the purpose of preparing anti-typhus vaccine, a number developed fever and a large percentage of the lice showed rickettsial infection. The organisms were extracellular and were said to resemble *R. pediculi*. It was stated that *Rickettsia* could be seen in the blood of the patient in large numbers. This is the first report in the literature in which large numbers of rickettsiae have been reported as being present in the blood of human beings. Such a statement must be regarded as unusual and has not yet been confirmed. Many authorities do not regard any of these organisms as Rickettsia.

Epidemic Typhus Fever

DEFINITION AND SYNONYMS

Synonyms.—Jail fever; ship fever; putrid fever; petechial fever; typhus exanthematicus. Ger. Fleckfieber; Fr. Typhus exanthematique; Sp. El tabardillo; Ital. Typho-esantematico.

Definition.—Typhus fever is an acute infectious disease caused by *Rickettsia prowazeki*. There is a fairly abrupt onset, with a continued fever lasting about 2 weeks, followed by a critical fall, or rather rapid lysis of temperature. About the fifth day a rose-spot eruption first appears about the loins and abdomen, later on extending over the trunk and extremities. The rash tends to become petechial and stands out rather prominently on a general cutaneous mottling. A stuporous state is a marked feature of the disease. It is transmitted by the louse, *Pediculus humanus*.

HISTORY AND GEOGRAPHICAL DISTRIBUTION

History.—Typhus fever has been one of the great epidemic diseases of the world. Hirsch notes that its history belongs to the dark pages of the world's story, at times when war, famine and misery of every kind are present. It is reasonable to suppose that many of the pestilences of ancient times and the Middle Ages were typhus fever. This disease was prevalent among the Spanish soldiers at the time of the conquest of Granada and the designation of the disease then used (tabardillo) is the one now given typhus fever in Mexico.

The disease was first described with sufficient accuracy by Frascatoro, in the 16th century, to enable us distinctly to differentiate it from plague;

the stuporous states of the two diseases having previously caused them to be confounded. In England, in the 16th century, the disease was very prevalent in the jails and court officials attending the trials of prisoners often contracted the disease and died; hence the designation "black assizes." During the Thirty Years War, in the 17th century, typhus fever spread over central Europe. Typhus fever was very prevalent at the time of the epidemic of plague known as the great plague of London, and it is a matter of practical interest that the two diseases were not infrequently confounded by medical men. The disease persisted in epidemic form throughout the duration of the Napoleonic wars and did not begin to subside until the conclusion of peace in 1815, after the battle of Waterloo. This epidemic of typhus fever was said to have been the severest one ever recorded on the continent. The general poverty and distress, which resulted from the war, evidently aided greatly in the spread of the disease not only among the troops but throughout the civilian population.

In earlier years, from the 16th to 19th centuries, numerous epidemics occurred in England, but in recent years the disease has greatly decreased. During the period 1884 to 1898 there were 2,249 cases, but from 1899 to 1913 there were only 390. In Ireland there were very severe epidemics in earlier years. During the 19th century there were six fever epidemics and outbreaks are still liable to occur in some districts of Ireland which are regarded as endemic centers.

In the United States and Canada typhus also prevailed in certain centers during the 19th century and there were severe epidemics following the Irish immigrations in 1846–47. In Mexico the disease became epidemic in 1530, shortly after the Conquest. During the 19th century also there were numerous epidemics, with a high mortality reported, from tabardillo, the Mexican disease. In South America, typhus was probably imported from Spain to Peru at a very early period, where it became well known under the Spanish name of tabardillo. It continues to prevail in this country and Chile at the present time.

Serbian and Other Epidemics.—Epidemics of typhus have very frequently been associated with war. In fact, severe epidemics have occurred during practically every great war in Europe with the exception of the Franco-Prussian war in 1870. In the World War, the epidemic which raged in Serbia in 1915 was one of the most severe which has occurred in modern times. It was characterized not only by its magnitude but by its high virulence and high mortality. During the height of the epidemic the number of new fever cases entering the military hospitals alone, reached as high as 2500 per day, and the number of reported cases among the civilian population was approximately three times this number. The mortality during the epidemic varied at different periods in different localities between 30 and 60 per cent, and in complicated cases sometimes reached 70 per cent. Over 150,000 deaths occurred within 6 months, before the epidemic could be suppressed. Coincident with the epidemic of typhus there occurred an epidemic of relapsing fever.

Poland has for many years been recognized as an endemic center of typhus. The disease became epidemic again in 1916 when the chief area at first affected was the governmental district of Warsaw, at the time occupied by German troops. In this district, which had a population of nearly two and a half million, 26,099 cases were

reported in about 12 months. In Congress Poland and Galicia combined, the cases reported for 1916 were 34,538. The measures taken against the epidemic in 1916 and 1917 failed to check its spread, but the hope was expressed that the epidemic would disappear in the summer months. The summer of 1917, however, seemed to have little effect in reducing the number of cases of the disease and in the year 1917 they numbered 43,840. In 1918, when Poland became an independent state, an extensive anti-typhus campaign was initiated. During the first year there were some 231,000 cases notified, with nearly 20,000 deaths, the mortality, however, being only 8.6 per cent.

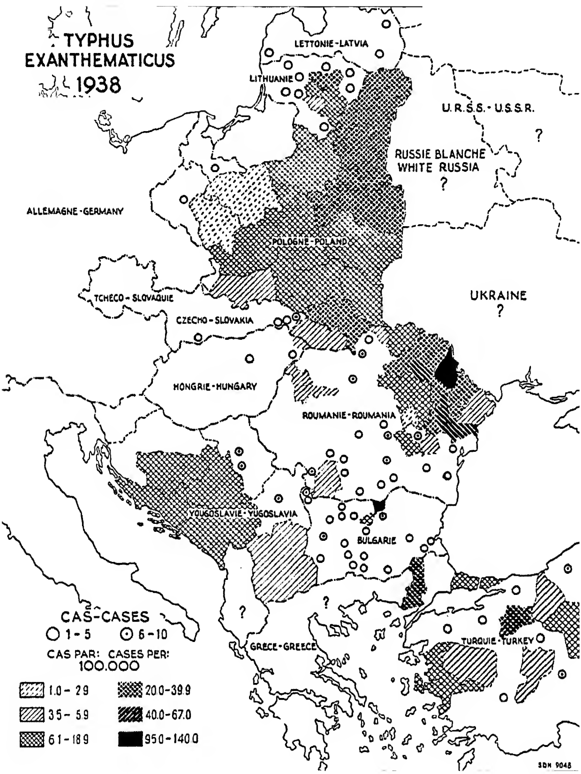

FIG. 207.—Typhus fever. Cases reported per 100,000 population in Eastern Europe in 1938. (Epidemiological Intelligence Service of the League of Nations.)

At the close of the World War, an extensive epidemic broke out in Russia and Rumania. In Rumania it caused some 800,000 deaths. In Russia, while there were no accurate statistics obtainable, it was estimated that some 5,000,000 cases of typhus fever occurred between 1919 and 1922. The epidemic, however, was apparently not of great virulence. In neither the Polish nor Russian epidemics was the percentage mortality as high as in the Serbian outbreak. Other outbreaks occurred at the close of the World War, especially among Greek and Armenian refugees.

During the Italian campaigns in Abyssinia in 1935, Castellani reported that there were at least 20,000 cases of typhus among the Abyssinian troops, but not a single case developed in the Italian troops because of the rigorous cleanliness enforced, it being exceptional to find an Italian soldier who was verminous. There were also, he states, in the Abyssinian army some 20,000 to 30,000 cases of relapsing fever, but only 17 cases were reported in the Italian troops.

Typhoid fever and typhus fever were only separated clinically as distinct diseases by Gerhard in 1837. Huxham, however, had previously noted the marked difference between the "putrid malignant fever" and "slow nervous fever." Until very recent times, it was declared that typhus fever was among the most contagious diseases of man and innumerable instances were cited of frequent contagion of those attending or visiting typhus patients. In 1909, Nicolle, in North Africa, demonstrated that the disease was transmitted by lice, and the experiences in the Balkan war and in the Serbian epidemic of 1915 show that in the absence of such vermin the disease does not appear to be contagious.

The late Sir William Osler remarked that the gradual disappearance of the disease in Great Britain and on the continent has been one of the great triumphs of sanitation and this also proved to be the case in connection with the epidemic in Serbia. It will be recalled that the Serbian epidemic of typhus fever was the first extensive and serious one to occur since the demonstration of the method of the transmission of this disease by lice in 1909–10. It should be emphasized that the efforts of all of the physicians, sanitarians, nurses, and particularly of the people generally in Serbia being directed against the spread of the disease by pediculi, the suppression of the epidemic by intensive work was accomplished within a period of six months.

Geographical Distribution.—Europe has been the principal center of the great typhus epidemics of the world. There have been recognized for many years two major endemic foci, the Union of Soviet Russia and Poland. For many years, before the World War and the Russian Revolution, there were from 50,000 to 80,000 cases of typhus reported annually in Russia, where the hygienic conditions were usually bad and there was overcrowding of jails with political prisoners, much poverty, many movements of the population on a large scale, and frequent wars. Although numerous endemic foci still persist in this country, through recent public health campaigns the situation has been somewhat improved.

The epidemics that occurred in Russia, Rumania and Poland after the World War have already been referred to under *History*.

After about a decade of steady decline in the prevalence of typhus throughout the world, the disease during the period 1933–40 has shown a notable increase in several countries. This new wave apparently reached its peak in 1933 in Egypt and in Chile, and in 1934 in South Africa and in most of the countries of eastern Europe. In 1934 and 1935 the disease was especially severe in the Soviet Union. It also was prevalent in Rumania, Poland, Yugoslavia and Portugal in 1934–35. The disease usually reaches its height in Poland and Rumania in April or May. During the years 1935–39 the number of cases did not rise above 700 as a maximum, and in the winter months has been below 100. In Rumania, since 1935 the disease has greatly decreased, from a maximum of 1600 cases in 1936 to below 100 in 1939. However, from Jan.–Sept. (1942), 3,400 cases were reported.

During 1941–42 the European reports from some areas are not available or reliable as in Russia and Germany. In Germany, Jan.–June (1941), only 1,015 cases and for 1942, only 2,732 cases were reported and in Hungary 713 cases. For January–April, 1943 there were 973 cases, while in the Union of Soviet Socialist Republics only 67 cases for this same period. More reliable figures from Spain show Jan.–June (1941) 4,367 cases and Jan.–Sept. (1942), 3,870 cases; in Turkey for the same period, 270 cases.

Typhus has also appeared recently in sporadic or epidemic form in Asia Minor, Syria, Palestine and all the countries of North Africa. Until quite recently, Equatorial

Africa was free from louse-borne typhus, but in 1932 an outbreak of the disease occurred in Uganda, especially in the sections of the district lying above 5400 feet. Typhus has also appeared in epidemic form in Urundi, Union of South Africa, Basutoland, and in the Transvaal. Epidemics also occurred in North Africa in 1937–38 and in the latter year in Morocco. In North Africa, Jan.–Sept. (1942) the following significant figures were reported: Algeria, 34,550; Egypt, 22,550; Morroco, 25,580; Tunis, 15,850. An increase has occurred in 1943, in Egypt 40,000 cases being reported. An outbreak of some 460 cases occurred in Italy in 1944.*

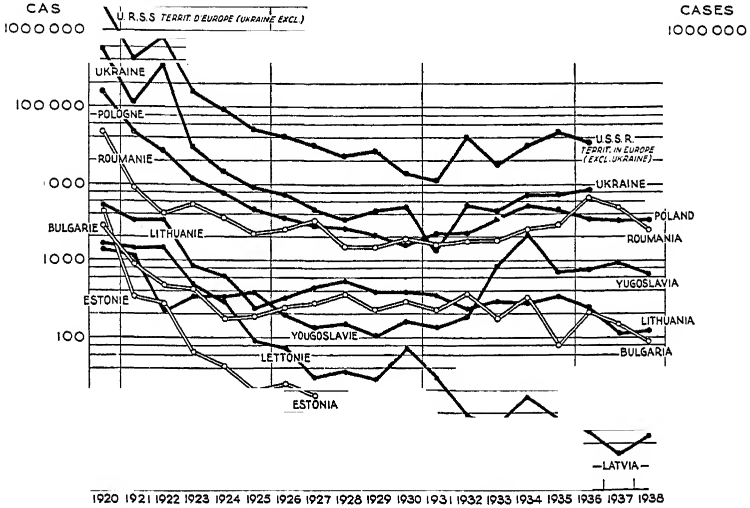

FIG. 208.—Typhus fever. Trend of typhus morbidity in Europe, 1920–1938. (Epidemiological Intelligence Service of the League of Nations.)

In Asia, the affected areas have been in the northern half of the continent, and the disease extends southward to the mountainous parts of Iran, Afghanistan, British India, southern Indo-China, and southwestern China. During 1941–1942 typhus in Central and South America has been especially noted in Bolivia, Chile, Columbia and Guatemala, and to a less extent in Mexico (1942). In Guatemala, Jan. (1941)–June (1942) some 2,000 cases and 477 deaths were reported. Plotz (1942) has shown from serum reactions that this outbreak is apparently of the epidemic type of typhus. Patino-Camargo has also shown that the outbreak in Bolivia was due to *R. prowazeki* and Groot (1941) that the epidemic in Columbia also was due to the classical louse borne strain of virus.

There has been no epidemic of the classical European louseborne typhus in the United States in recent years. The Philadelphia epidemic, 1836–7, was of special note, since it was in connection with it that Gerhard first differentiated the disease from a clinical standpoint from typhoid fever.

In the course of the 19th century, several epidemics of moderate size occurred in a number of the American seaports and along the Atlantic Coast to the north of Mexico, which apparently originated among affected Irish immigrants. The last report of epidemic typhus in Philadelphia was in 1883. Flippen (1938) however, has reported that endemic typhus has been present there, some 27 cases having been recorded since 1911. The largest outbreaks in New York of this nature were in 1892 and 1893. Since this date, only a few cases of typhus have been detected among immigrants which were held in quarantine. However, the louse-borne infection of Mexico, tabardillo, has occasionally been brought northward into the United States, resulting in outbreaks of the disease in Iowa (1917) reported by Boyd; in California, reported by Cumming and Sefton; and in New Mexico, 1922, reported by Armstrong. Sporadic cases of mild typhus (known as Brill's disease) still appear from time to time, especially in New York City, and endemic murine typhus occurs especially in the southern United States.

* Brigadier General Fox (1944) has reported the control and termination of this outbreak by the United States of America Typhus Commission.

(These types are discussed on p. 953.) Small numbers of sporadic mild cases of typhus have also been reported by Hone from Adelaide, Australia.

ETIOLOGY

For many years the true etiology of typhus fever was unknown. A number of different bacteria, both bacilli and cocci, were in earlier years described by a number of investigators as the cause, but none of these claims were substantiated. The infectious nature of the disease was

FIG. 209.—*Rickettsia prowazeki.* × 1200. Section. Junction of oesophagus and mid gut of louse. The epithelial cells of the oesophagus not infected. The epithelial cells of the mid gut greatly swollen and heavily infected with rickettsiae. Near the base of the membrane of the gut on either side of the oesophageal orifice are small groups of bacilliform rickettsiae. (Preparation of Wolbach. Courtesy Harvard University Press.)

well recognized, but the gross pathological lesions encountered at autopsy, such as enlargement of the spleen with parenchymatous degeneration of the viscera, were obviously not characteristic. The discovery of specific histological lesions by Fraenkel in 1914 did not reveal the cause, nor did the study of microscopical preparations from viscera and of cultures upon bacteriological media reveal any specific microorganism. Later the blood was found to be infective for guinea pigs and monkeys (Ricketts, Nicole, Anderson, and others). Some of these infections were

produced with filtrates of material containing the virus, notably by Nicolle, and for a time some observers believed that the disease might be classified with those due to the filterable viruses. However, Ricketts (1909–10) reported the presence of visible organisms in the blood of man and in the blood of monkeys and guinea pigs inoculated with human infected blood, as well as in infected lice that had bitten cases of typhus fever, and of ticks that had bitten cases of Rocky Mountain Spotted fever. Rocha-Lima, in 1916, also encountered and described "rickettsiae" in lice which had fed on human cases of typhus. Shortly afterwards, other rickettsiae, or rickettsia-like organisms, were found by a number of observers free in the intestines of normal lice, as well as in lice which had bitten patients with other febrile diseases. This led many observers to hesitate regarding the suggestion of the etiological nature of *Rickettsia prowazeki* in typhus fever. However, further proof of this fact was given by Wolbach.

Wolbach and his associates, Todd, Palfrey and Pinkerton, in a study of Typhus in Poland in 1920–22, found that intracellular *Rickettsia prowazeki* occurred only in lice (and in a large percentage of them) after they had been allowed to feed on typhus cases. They also found from histological studies of tissues of human beings who had died of typhus the same organism localized almost exclusively in the vascular endothelium. The reaction to the Rickettsia was shown primarily by degenerative changes giving rise to thrombosis in blood vessels and by a proliferative reaction on the part of the endothelium and neuroglia, which gave rise to the characteristic microscopic "nodules" of the disease in the skin and central nervous system. From these investigations and, later, confirmatory work, the evidence that *Rickettsia prowazeki* is the etiological factor in typhus fever would appear to be definite.

The cultivation of *Rickettsia* is discussed on p. 924.

Transmission.—Epidemic typhus fever is transmitted by the louse, *Pediculus humanus*. Ricketts (1906) first demonstrated the experimental transmission of the rickettsial disease, Rocky Mountain spotted fever by inoculation of the blood into guinea pigs and monkeys. He also showed that it was possible to transmit this disease by infected wood ticks, and the following year showed that the virus was transmitted hereditarily in the tick. In 1909 he reported the presence of the micro-organism causing the disease in films of the blood of man and of the monkey and guinea pig and in the tissues of the tick.

Nicolle, Conte and Conseil (1909) working in Tunis, first showed by actual experiment that the chimpanzee could be infected with typhus virus by the injection of a small amount of blood from a human case in the active stages of the disease. They then showed that lower monkeys could be similarly infected by the inoculation of the chimpanzee's blood and that the infection could be transmitted from monkey to monkey by means of the bites of the infected body louse (*Pediculus humanus* var. *corporis*). This work was shortly afterwards confirmed in the United States by Ricketts and Wilder (1910) and by Anderson and Goldberger (1912).

Ricketts also demonstrated the transmission of Mexican typhus, or tabardillo, by the louse. He reported the presence of the micro organism of the disease in blood films of the patients and of the intestinal contents of infected lice and showed by cross-immunity experiments that typhus and Rocky Mountain spotted fever are two distinct diseases and that the flea and bed bug are not concerned in the transmission of Mexican typhus.

From other experimental work performed first by Goldberger and Anderson, it seems clear that *Pediculus capitis*, the head louse, may also sometimes transmit the disease experimentally. However, it is not regarded as an important agent of transmission during epidemics.

It has also been demonstrated that monkeys may be infected by the inoculation of crushed lice, or with the faeces of infected lice. The causative agent, *Rickettsia prowazeki*, does not invade the salivary glands of the louse but is discharged during the active feeding in great numbers in its excreta. Probably the infection occurs through the bite puncture becoming soiled with the faeces, or by scratching. Arkwright and Bacot (1923) reported that the virus may survive in the excreta of infected lice at room temperature for 11 days.

EPIDEMIOLOGY

Formerly typhus fever was regarded as the most contagious of all diseases. We now know that in the absence of the body (and head louse) the disease is only slightly if at all dangerous to those who come into contact with the patient. At the same time, experience has shown that it requires the greatest care on the part of those having charge of louse destruction to avoid being infected while attending to this duty. The same is true of those examining patients with the disease prior to the eradication of the body-lice of the sick.

There is no definite evidence that the sputum or other discharges of a patient with epidemic typhus carry the infection. In the study of the epidemiology of typhus cases in Georgia and Alabama, Maxcy could find no evidence that the louse played a part in the transmission of the disease, and he suggested that there might be a rat or mouse reservoir of virus from which the disease was transmitted to man. These cases were sporadic and there was no evidence of contact infection. Clinically the cases were mild typhus and they gave a positive Weil-Felix reaction. The seasonal incidence of this small outbreak was in the summer months—just the opposite of the Old World typhus, which is most prevalent towards the end of winter. We now recognize this form as endemic typhus, or flea-borne, or murine typhus.

The Transmitting Agent.—In connection with the epidemiology of epidemic typhus, a knowledge of the life history of the body louse is necessary. The body louse, *Pediculus humanus* var. *corporis*, (*Pediculus vestimenti*) is slightly larger than the head louse, *P. humanus* var. *capitis*. It is the species concerned in the transmission of Indian and North African relapsing fevers and trench fever, as well as typhus fever, although it is probable that the head louse can also transmit these infections.

While the head louse lives among the hairs of the head and shows its presence chiefly by the appearance of its pear-shaped eggs (nits) projecting from the hair shaft, the body louse attaches itself to the under surface of the garments worn next the skin and holding

fast to the undershirt feeds about twice daily on the human host. It is but rarely found on the skin. The female body louse is about 1/7 inch long and about 1/15 inch broad (3.5 mm. × 1.5 mm.). The antennae are somewhat longer than those of the head louse. Deprivation of food causes death of the adult in 9 days and the newly hatched louse in 2 days.

The female, under favorable temperature conditions (65°F.), begins to oviposit three or four days after reaching maturity, and thereafter, during her average life of four or five weeks, lays four or five eggs daily.

The eggs, when on clothing next the body, hatch out in 7–10 days, and become mature in about two weeks. There is no grub stage as with the fleas.

As the eggs are usually deposited in inaccessible portions of the clothing, as in the seams, and since they remain viable there for more than a month, infested clothing should be steam-treated before being worn.

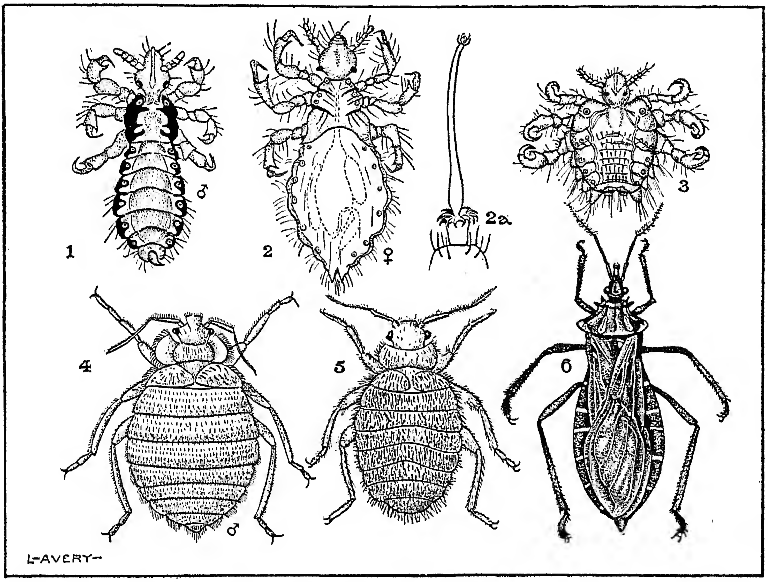

FIG. 210.—Anoplura and Hemiptera. 1. *Pediculus humanus* var. *capitis*. 2. *Pediculus humanus* var. *corporis*. 2a. Protruded rostrum of *Pediculus*. 3. *Phthirus pubis*. 4. *Cimex lectularius*. 5. *C. rotundatus*. 6. *Triatoma megista*.

Anatomy.—The *body louse* is somewhat larger than the head louse, and there is less marked festooning of the sides of the abdomen so that the segments are less well marked. The head is separated from the thorax by a narrow neck, there being but slight differentiation between the thorax and abdomen. The head is rather olive-shaped and more pointed anteriorly, where is situated the mouth surrounded by a hook-bearing ring (the haustellum). The five-jointed antennae are attached to the side of the head. The three stylets are inside the mouth and are long and sharp. They can be protruded through the mouth orifice and when apposed make a tube through which the secretions from the salivary glands empty. These needle-like stylets make the wound which causes the blood to flow. The blood is sucked up by the pharynx which lies above the stylets and has muscular walls making it a pumping organ. From this a narrow oesophagus leads into the long prominent stomach which terminates in a narrow S-shaped hind-gut. The tracheal system (respiratory) opens along the sides of thorax and abdomen in round openings or spiracles. These can be closed by oils, thus asphyxiating the louse. The female has a pouch-like opening beneath the hind-gut

which leads to the oviduct which connects with two ovaries. The eggs receive the cement material in the oviduct.

As the body and head louse differ more in habit or location than in structure and will interbreed readily, they are generally regarded as varieties of the same species, i.e., *Pediculus humanus*, varieties *capitis* and *corporis*.

The lice will usually leave the human host only when he has fever or when he dies, but they of course may drop off or be brushed off. They are not apt to be found in the bedding. Those who bathe and change the underclothing frequently do not become louse infected, though there is always the possibility that an occasional louse may gain access to the body and perhaps transmit typhus infection.

Pediculus Humanus var. Capitis (*Pediculus Capitis*).—The eggs, usually 60 in number, are deposited on the hairs of the head, the favorite region being back of the ears. They hatch out in about six days. The lice larvae on emergence closely resemble the adult and begin to feed shortly after hatching. They moult about every three days and become adults within ten days.

The adults vary in color according to the color of the hair of the host. The thorax is as broad as the abdomen. The male louse is smaller, is rounded off posteriorly and shows a dorsal aperture for a pointed penis; while the female is recognized by its larger size, 2 mm. in length, and by a deep notch at the apex of the last abdominal segment.

There seems to be a marked preference exhibited by lice for their own peculiar racial host.

A great many physicians of different nationalities died from typhus during the World War, and a great many more contracted the disease. In many instances these physicians were thoroughly cognizant of the common method of transference of the disease by lice and of the precautions to be taken in avoiding such infection. In a number of instances where particular care was taken to avoid contamination with lice, nevertheless infection with typhus followed. For this reason, it has been particularly urged that infection must sometimes occur in man by another manner than through the agency of pediculi, and it has been suggested that the droplet method of infection, after coughing, might sometimes occur in this disease. It is recognized that in the early stages of typhus there are likely to be inflammatory conditions of the mouth, nose and throat. As yet, however, there has been no experimental proof that the sputum or saliva in typhus fever contains the virus. It has been reported that certain infections in the laboratory have occurred in workers who have acquired the infection from the spraying of emulsions from infected lice into the eye, and there is also evidence that infection from louse excreta can enter through slight abrasions of the skin or by inhalation.*

Blanc and Baltazard (1938) have reported that infection from typhus can be produced by placing dried flea excreta on mucous membranes, and they believe that infection through the mucous membrane may be a frequent method of transmission of murine typhus.

They made attempts to infect 6 individuals with dried excreta of infected fleas, placing 20 milligrams on the nasal mucosa of 2 men and 5 milligrams on the conjunctivae of 2 others. Two others were given the dried excreta dissolved in water to drink. One of the men inoculated by the nasal route developed fever. There was no apparent

* Some 25 such laboratory infections have been reported in individuals that had been thoroughly vaccinated. A considerable number of cases of infection by inhalation of rickettsiae from dried louse feces in clothing have been reported at delousing stations in Germany during 1943.

reaction in the 5 others. However, when these 5 were tested 65 days later by the injection of living virus, 3 were found to be immune. Therefore, they thought that at least 4 of the 6 men had been infected. They have reported that the dried excreta of infected lice or fleas may retain its virulence for at least 12 months, and suggest that louse-borne typhus infection may also occur by the oral route, or by dried louse excreta. Violle (1938) has also succeeded in infecting animals by feeding them infected material. Sparrow (1935) and Mareschal (1939) have also shown that infection of guinea pigs and of man may occur through the nasal mucosa with living murine virus.

There is good evidence that the virus of murine typhus is present in the urine of infected rats, and Nicolle (1934) and Lechuiton (1938) believe that man can be infected through the ingestion of foods soiled with rat urine, since animals may be infected with murine typhus through the ingestion of material containing the virus. The transmission of endemic typhus is considered on p. 955.

Climate.—In epidemic typhus the disease is most frequent in the winter and early spring, often diminishing, or in some instances disappearing entirely during the summer. The heavy clothing worn in winter affords the opportunity for breeding of lice, while crowding by the people in their houses in winter and in their sleeping quarters facilitates the transmission of lice. Warm, padded, and fur-lined clothes and flannels furnish especially favorable breeding facilities for lice, which live especially in the clothing and only come to the surface of the body for feeding.

PATHOLOGY

Fraenkel, in 1914, first called attention to the specific lesions, consisting of proliferative changes in the endothelium of the arterioles and arterial capillaries, followed by necrotic changes. These changes are chiefly manifest in the vessels of the skin, central nervous system, and myocardium. In addition to the proliferation of the endothelial cells there is a perivascular infiltration of small round cells. Kurt Nichol noted that there was a combination of proliferative and inflammatory changes. The lesions are microscopical and there is absence of characteristic macroscopic findings. This proliferation of endothelial cells gives rise to small swellings somewhat resembling minute miliary tubercles and the perivascular infiltrations in the brain may suggest that seen in encephalitis. The perivascular infiltrations in the skin produce Fraenkel's typhus nodules and the microscopical examination of a small piece of skin may be diagnostic.

The petechiae are due to thrombosis of the smaller vessels and subsequent haemorrhagic manifestations. These important studies by Fraenkel were confirmed by Aschoff (1915), Chiari (1917), Jaffe (1918), Wolbach (1920) and others.

Morbid Anatomy.—The gross pathological lesions of typhus are not distinctive. The rash is often evident at post-mortem. Haemorrhages of considerable size may be present in the skin and subcutaneous tissues, especially in areas which have been subjected to trauma. Areas of skin necrosis or gangrene may be present. They are rarely accompanied by thrombosis of the large vessels, being due to extensive thrombosis of the capillaries of the small veins and arteries of the skin. Small haemorrhages in the conjunctivae are frequent. The heart usually shows slight gross

changes. Cloudy swelling is often present. Microscopically the blood vessels show similar lesions to those observed in the skin, and sometimes there is considerable infiltration with mononuclear and polymorphonuclear cells. Thrombi are rarely found in the larger blood vessels. In Wolbach's series of 39 cases, mural thrombosis of the aorta and iliacs was

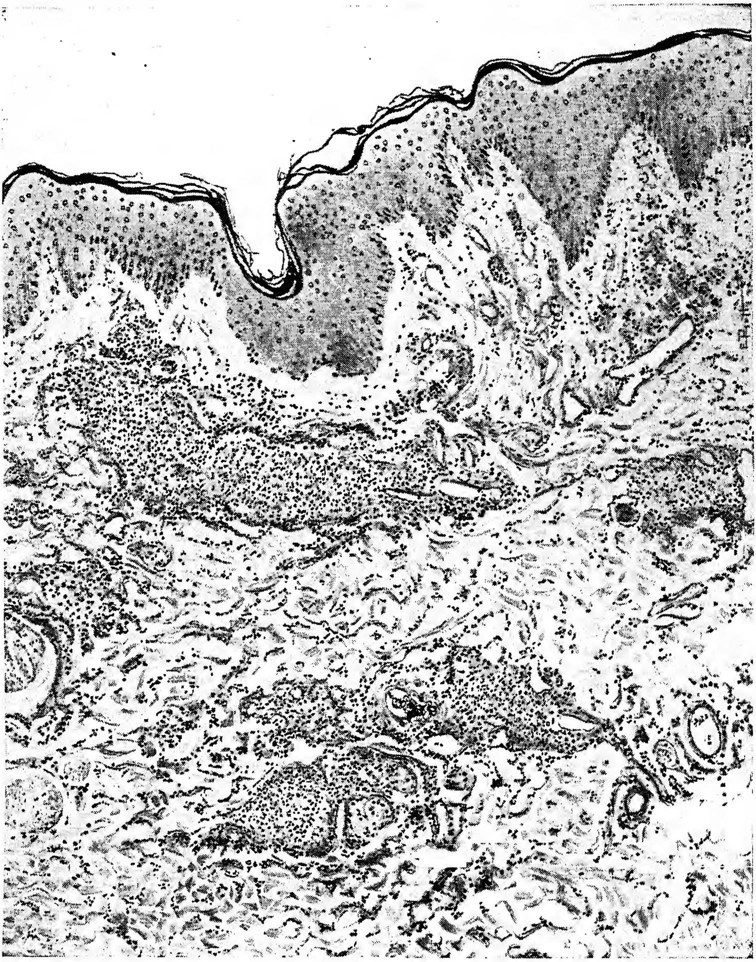

FIG. 211.—The skin from a case of Mexican typhus, showing the proliferative lesions, "typhus nodules," and a cross section of an artery with a thrombus. (Preparation of Wolbach. Courtesy Harvard University Press.)

observed and thrombosis of the mesentery, carotid pulmonary and splenic arteries was also noted as a rare lesion. In many of his cases, however, the microscopic examination of the vessels was necessary to demonstrate the lesions.

The blood is usually dark colored and the liver and kidneys show cloudy swelling. The spleen is somewhat enlarged during the early

stages of the disease but tends to be normal in size later on. It is often very soft and then may rupture from being handled at autopsy. Microscopically, engorgement with blood, with extensive phagocytosis of red blood corpuscles and diminution of lymphoid elements, is commonly present.

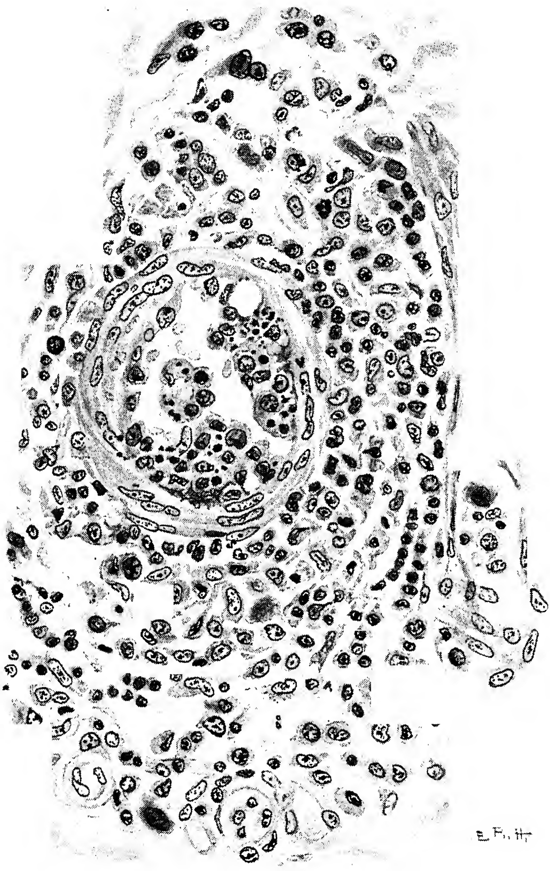

FIG. 212.—Arteriole of skin. Death in second week. Showing attached mural thrombi composed almost wholly of phagocytic endothelial cells. Perivascular reaction. 400 X. (Preparation of Wolbach. Courtesy Harvard University Press.)

Bronchitis and broncho-pneumonia are extremely frequent and constitute a most common fatal complication. In 8 of Wolbach's series extensive broncho-pneumonia was the immediate cause of death. The oesophagus, stomach and intestines are usually normal in appearance. There are no changes in the Peyer's patches and the mesenteric glands are not enlarged, thus differentiating from typhoid fever.

The parotid gland is frequently swollen, having become infected secondarily with bacteria from the mouth by way of the ducts. While the scrotal tissue may share in the general involvement of the skin in typhus, in contrast to the reports of Rocky Mountain spotted fever, the genetalia are affected but slightly. Only an occasional thrombosed vessel is found in the testes, with no lesions in the female genitalia.

The lesions in the brain, particularly in the basal ganglia, medulla and cortex of the cerebrum, and more rarely in the white matter and cerebellum, correspond in size to miliary tubercles and are secondary to lesions of the small blood vessels and capillaries, as in the skin. They first consist of a collection of large cells of vascular and perivascular origin, endothelium, and monocytes, with necrosis resulting from occlusion of the vessel. The further accumulation of cells derived in part from the proliferation of mononuclear phagocytes, and in part from neuroglia, results in the formation of cell clusters in the nervous tissue. The lesions are invasive, in contrast to the perivascular cell accumulations in the brain in most other infectious diseases. The number and wide distribution of these lesions are probably the cause of the severe nervous symptoms which have sometimes been ascribed to the toxic effect on the organism.

SYMPTOMATOLOGY

The period of incubation varies from 5 to 15 days. Usually, however, it is from 8 to 12 days. The period of onset may cover about 2 days, during which time the patient has headache, giddiness, backache, anorexia, perhaps nausea, and general malaise. There may be rigors or chilly sensations. About the end of the second day the temperature rises fairly rapidly to become 103° or 104°F. by the third or fourth day. With the rise of fever, the face becomes flushed, the eyes injected and the expression apathetic. The headache is usually quite severe and may be frontal, occipital or generalized. The temperature remains elevated, with slight morning remissions, for from 12 to 14 days, when it may fall by crisis or more gradually by rapid lysis.

Well-marked prostration and cardiac weakness are early noted. There is a tendency to constipation and the mouth becomes foul and the teeth rapidly covered with sordes, unless the greatest precautions in oral cleanliness are observed. There is marked tendency to clouding of the consciousness. At times the disease shows an abrupt onset rather than that described above.

The eruption appears from the third to seventh day. Usually it is present by the fifth day, consisting of slightly elevated rose spots, which at first disappear on pressure, but quickly tend to become permanent and later purpuric. The eruption first appears in the axillae, flanks, and then extends to the abdomen, chest and later to the extremities. The term mulberry rash is sometimes used to describe the rash of typhus. In addition to the above there is a subcuticular mottling. The conjunctivae are injected. Along with the appearance of the rash, the symptoms become aggravated, the effect on the heart is more marked, and the pulse

becomes feeble. The face is often dusky. There may be a bronchial catarrh with an annoying cough.

By the end of the first week, the delirious or stuporous condition becomes more marked, with a tendency to muttering delirium, tremors and subsultus, the coma-vigil of the older writers. Terrifying hallucinations may cause the patient to jump from the window and kill himself. There is a tendency to parotitis and otitis media, connected with the mouth condition. On account of the circulatory weakness, there is a tendency to gangrene of the extremities, especially the toes, rarely the fingers.

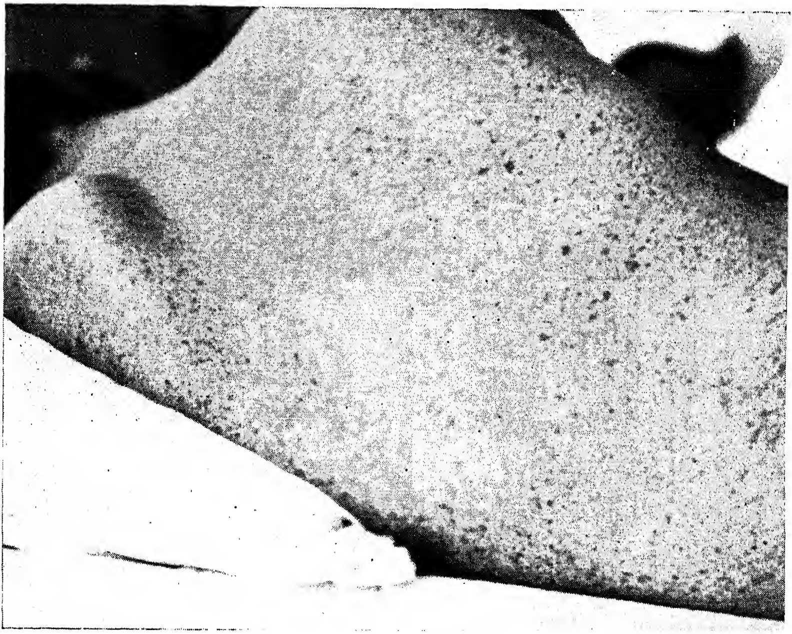

FIG. 213.—Erythematous and petechial eruption. Second week of typhus. (Preparation of Wolbach. Courtesy Harvard University Press.)

In cases which recover, there is a critical change in the apparently desperate condition of the patient about the end of the second week, the sudden striking change for the better being more marked in typhus fever than in any other disease. The temperature falls and there is abundant sweating. The stupor disappears, consciousness returns, and the patient frequently realizes the improvement in his condition. At this time the urine changes from a high-colored, often albuminous, one to an abundant secretion of more or less normal character. General weakness, however, with persistent circulatory disturbances may continue in some instances for a fortnight after the crisis. In other cases, in spite of the fall in the temperature, the mental condition remains unfavorable or becomes worse, changing from delirium to coma. Muscular twitchings appear, with

incontinence of urine and faeces, the case terminating fatally. In such instances the symptoms are probably due to the prevalence of wide distribution of the typhus lesions in the central nervous system

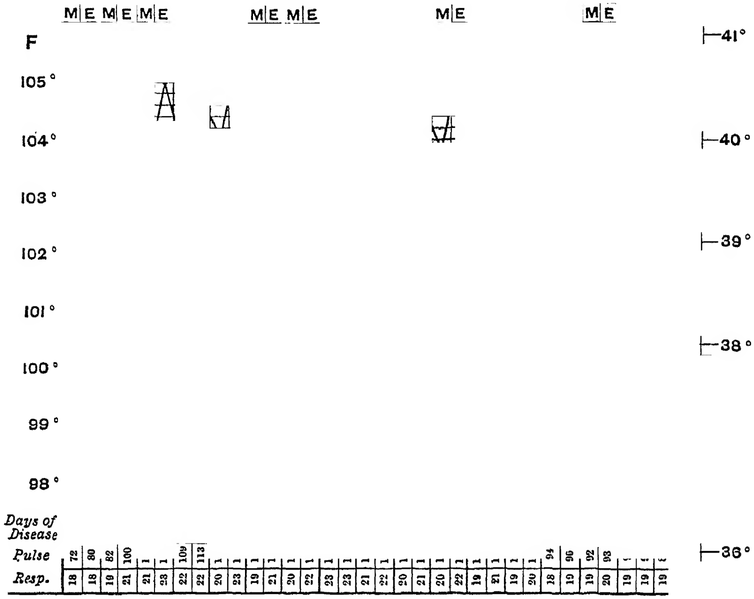

FIG. 214.—Temperature chart of typhus fever.

SYMPTOMS IN DETAIL

The Eruption.—This first appears about the fourth day as macules about axillae and loins, then spreading over abdomen, chest and back. It is often more pronounced on the back than elsewhere. It almcst never appears on the face, but may occur on the palms and soles. It has a resemblance to the rash of measles. At first disappearing on pressure, it soon becomes permanent and then petechial. The livid color of the rash has brought about the designation "mulberry rash." The rash lasts from a few days to two weeks. Markedly haemorrhagic rashes may be accompanied by haematuria, haematemesis, and melaena. In such cases, the mental symptoms are frequently severe and the cases are apt to be fatal.

The Fever.—The fever rise following a chill, is much more rapid than in typhoid fever, reaching its fastigium in about 3 days. A more or less continuous range of fever (103° to 104°F.) follows until about the fourteenth day, when there is often a rapid lysis, or possibly crisis, at which time the patient tends to fall into a refreshing sleep and to show a rather marked diuresis.

The Alimentary Tract.—Constipation is usually noted. Very marked is the tendency of the mouth and tongue to become dry and sordes to

collect on the teeth. The dry, black tongue has led to the designation "parrot tongue." It is often difficult to get the patient to protrude his tongue when told to do so.

The Circulatory System.—Very outspoken is cardiac weakness due to myocardial degeneration. The heart sounds are very weak and the pulse feeble, rapid, and irregular. The blood pressure often is very low, especially the diastolic, and may remain so throughout the disease. Bradycardia may be marked during convalescence.

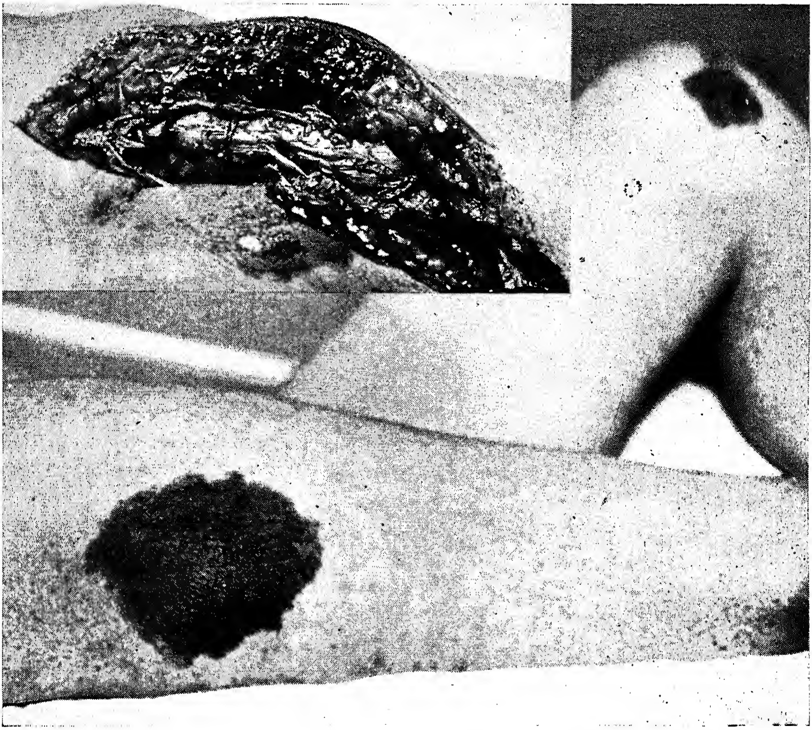

FIG. 215.—Necrosis of the skin and subcutaneous fat over right trochanter and left condyles of the femur. Insert shows an incision made after death through the lesion over the trochanter. (Courtesy Harvard University Press.)

The Respiratory System.—Cough may appear in the first days, but usually is first troublesome about the time of the eruption. By the end of a week, the cough becomes loose and rales of various types may be noted. Death often occurs from a terminal broncho-pneumonia.

The Nervous System.—Clouding of the consciousness may be as marked in this disease as in plague. Dull aching frontal headache is common and is an early predominating symptom. It frequently diminishes before the eruption appears. A dull stuporous state soon comes on. Delirium is marked in some cases. As in plague, there are often the facies and mental state of alcoholic intoxication. There may be rigidity and

retraction of the neck, suggesting cerebrospinal fever. However, there is usually only a slight increase of mononuclear cells in the spinal fluid, and the fluid is not markedly turbid.

The Blood.—There is nothing very characteristic in the blood examination. The leucocyte count sometimes falls in the first day or two, then gradually rises until the crisis, and then again falls. The leucocytosis is only moderate, it rarely exceeds 12,000, and the polymorphonuclear cells make up about 80–85 per cent. Eosinophiles are decreased. Some observers have noted an increase in the large mononuclears.*

Complications.—A bronchitis is very common and later on there may be such a profuse expectoration that it is difficult for the patient to expel it and he may become cyanotic. Bronchopneumonia is a very frequent cause of death. Otitis media and parotitis are not infrequent complications. Deafness is often marked. Retention of urine is not uncommon. Incontinence may occur during the delirium. Febrile albuminuria, and cylindruria, are usually present, but nephritis is rare. Thrombosis of various vessels, both abdominal and peripheral, may be noted. Gangrene of the extremities, especially the toes, is frequently present. Gangrene of areas subjected to pressure, as over the sacrum, is not infrequent. Symmetrical gangrene of the extremities was observed by Shattuck in the Serbian cases. There does not seem to be the same tendency to gangrene of the genitalia as in spotted fever of the Rocky Mountains. Shattuck found that during convalescence suppurative lesions such as abscesses were not uncommon. One patient developed suppurative lesions about the knee joint, followed by an abscess near the thyroid. A perinephritic abscess was a late sequel in one case. Small boils were common, and suppurative otitis media and mastoiditis were observed not infrequently. He found that even after the most severe symptoms convalescence was rapid, considering the emaciation and weakness of the patient. Pain, more or less severe, in the legs and feet was a very common symptom of convalescence. In a few cases rapidity or irregularity of the pulse persisted for a considerable time.

DIAGNOSIS

Differential Diagnosis.—The disease must be distinguished from typhoid fever, malaria, relapsing fever, and Rocky Mountain spotted fever. Prior to the appearance of the rash, a differential diagnosis is frequently impossible. However, during an epidemic the diagnosis is often fairly evident from the onset of the fever chill and headache. The more gradual course of the fever and the less marked stuporous condition, together with a positive Widal reaction and positive blood culture, should differentiate typhoid fever from typhus.

Plague has the same picture of alcoholic intoxication as typhus, but the characteristic rash is not present. Influenza, with its acute onset, is confusing, but there is not any increase in the number of leucocytes.

In encephalitis lethargica there is no eruption and no splenic enlargement, and the onset is gradual, with only moderate fever.

* Snapper has found that when the skin rash has persisted for a considerable period it might be connected with thrombopenia. In one case the blood platelets were only 15,500 per cm. (Chinese Lessons to Western Medicine, 1941.) Lampert, who has studied 300 cases, in daily observations of the blood, found during the first few days there was a pronounced shift to the left in the Arneth Schilling index. He concluded that at this stage when the percentage of the neutrophiles with rod-shaped nuclei (stabs) was 25–40, this was diagnostic of typhus.

Relapsing fever and malaria are satisfactorily differentiated by the blood examination. In both, also, the spleen is more apt to be enlarged.

The distinction between endemic typhus and spotted fever may be difficult on clinical and epidemiological evidence. The clinical course, however, is generally more severe in spotted fever and in epidemic typhus than in endemic typhus.

In Rocky Mountain spotted fever a history of tick bite may be of assistance, and sometimes a small ulcer may indicate the site of the bite. Pinkerton (1940) points out that the differentiation may be made in the laboratory by cross immunity tests, in the inoculation of guinea pigs, and by the fact that typhus rickettsiae grow voluminously in the cytoplasm in the cells of tissue cultures but never invade the nuclei, while spotted fever rickettsiae, regardless of how atypical the strain from which they are derived may be, grows sparcely in the cytoplasm but form compact, spherical colonies in the nuclei of the infected cells. These distinctive patterns are also found in the cells of infected arthropod hosts, the tick and the louse, of these two viruses.

The differentiation between epidemic or European and endemic or murine typhus may be made on the basis of lack of an obvious scrotal reaction with the European strain, on guinea pig inoculation, and from the fact that murine typhus causes a febrile disease in the rat, with Rickettsiae in the scrotal sac, while the European typhus virus causes an entirely inapparent infection in this animal.

Weil-Felix Reaction.—In the diagnosis of typhus fever, great importance is attached to the Weil-Felix agglutination reaction which the serum of typhus patients has upon certain proteus bacillus cultures designated as OX2 and OX19. These correspond in characteristics to certain strains of *Proteus vulgaris*, producing indol in peptone solution, and acid and gas in glucose, maltose and saccharose, but not in lactose or mannite. They digest gelatine and blood serum somewhat more slowly than typical cultures of *Proteus vulgaris*. Although these organisms have been isolated from the urine of several typhus cases, it seems certain that these X bacilli are neither causative organisms nor secondary invaders. The reaction is therefore heterologous and not specific. The reaction appears during the first week of the disease, but becomes quite marked in the second week and during convalescence. Thus a titer of 1 to 25 on the fifth day usually rises to 1 to 200 or higher by the end of the second week. The test is made either with living or dead cultures and is carried out as for typhoid agglutinations, preferably by the macroscopic method.

The Weil-Felix Agglutination Test.—The Proteus culture recommended by Weil and Felix, and universally used, is one isolated in 1916 from the urine of a typhus case, and known as Proteus X19. In a study of dissociation forms of this organism two forms were recognized, a motile, flagellated type (H) and a non-motile, unflagellated type (O). It is this latter type, or Proteus OX19, that is the standard culture. Other Proteus strains used for agglutination tests are OX2 and OXK. It is strange that the guinea-pig, infected with Rickettsia, fails to show serum agglutinins although protected from virulent doses of rickettsial material. Precipitins and bacteriolysins are also absent.

The test should be performed macroscopically. Serum dilutions of 1 to 25 and even 1 to 50 may fail to agglutinate (proagglutinoid zone) whereas higher dilutions (1 to 100 or 1 to 200) will show agglutination. Agglutinins are demonstrable by the end of the first week, and the titer rises during the course of the disease, often reaching 1 to 2000 at the termination of the fever, after which it steadily falls. A titer of 1 to 80 or less has no significance; 1 to 160 is suggestive; 1 to 320 or 1 to 640 is usually but not invariably diagnostic. Titers as high as 1 to 40,000 have been reported.

The Journal of the R.A.M.C. in an editorial (March, 1935) states that a classification of rickettsiae according to their vectors is unsatisfactory, and advocates a classification based on antigenic relations. The following table, based on the work of Felix, is given:

	Epidemic typhus	Tsutsugamushi	Rocky Mountain spotted fever
X19	+++	−	+
X2	+	−	+
XK	−	+++	+

Bridges (1935) has noted that while the O variety of X2 is extremely stable this is not the case with these variants of X19 and XK, which tend to change to H variants. He points out the difficulties of maintaining standard cultures even in great national laboratories, and emphasizes the advantages of killed suspensions over the living organisms. Bridges recommends killing with alcohol, then removing the alcohol and resuspending in saline, then preserving with buffered formol saline, with the concentration of the formalin 0.25 per cent.

Although Felix has reported the cultivation of Proteus X19 from the blood and organs in typhus, there is little evidence either from *systematic* blood and urine cultures performed during life or from the organs post-mortem that this bacillus is the etiological factor in typhus. For a time the hypothesis was suggested by some that rickettsiae represent mutants of *B. proteus*. This view, however, is no longer regarded as correct. Anigstein, in his attempts at cultivation of rickettsiae, obtained certain appearances of growth which led him to believe that a close connection existed between rickettsiae and *Bacillus fusiformis*. This view is also no longer held tenable. However, no satisfactory explanation of the significance of this reaction in typhus fever is known. The only suggestion of its explanation has been furnished by Zinsser, Castaneda and Zia, who have found a common antigenic factor, probably a carbohydrate, in proteus OX19 and in suspensions of murine rickettsiae.

The National Institute of Health, and Plotz in the Army Medical School, Washington, regard a rise in titer of greater significance than any 1 reading, unless it is above 1260. A slide agglutination test has also been suggested with Proteus and also with a rickettsial antigen. Van Rooyen and Bearcroft (1943) in the agglutination tests in the British Middle East forces in Egypt have used rickettsiae suspensions prepared by Craigie of Toronto which were remarkably stable and consistent in their responses. Concentrated rickettsiae vaccines constitute a satisfactory antigen either for use in the complement fixation or agglutination test.

Complement Fixation.—Employing specific rickettsial antigens complement fixation tests can now be performed to distinguish between the various rickettsial diseases. Castaneda, and Bengtson and Topping have reported such a test for endemic typhus, Bengtson for Q fever, and Plotz and Westman for Rocky Mountain spotted fever. Plotz has recently developed an epidemic rickettsial antigen so that positive fixation is obtained in epidemic typhus. Furthermore by means of the complement fixation test he is able to distinguish between epidemic and endemic typhus, and has also shown that Brill's disease belongs to the epidemic typhus fever group. (Personal communication. See also Science, 97, 20, 1943.)

PROGNOSIS

The mortality has varied greatly in different epidemics, from as low as 5 or 10 per cent to 70 per cent. A mortality of 20 to 35 per cent is not uncommon. During the Serbian epidemic (1915) it reached 70 per cent, but in other more recent outbreaks in eastern Europe it has been as low as from 8 to 12 per cent. In some of these the virus may have been that of endemic murine typhus. In endemic typhus of the United States, the mortality is estimated by Maxcy to be between 2 and 4 per cent.

The mortality in epidemic typhus is greatly influenced and increased by lack of proper nourishment and nursing and care given the patients. The mortality usually increases with age. In children, it is a very mild disease and death rarely occurs in individuals under 20 years of age, except in severe general epidemics. In later life the liability to severe bronchopneumonia which results fatally is more common. Old people are generally apt to succumb.

The prognosis is serious in cases with high fever, profuse rash and marked mental disturbances.

Typhus fever has claimed more victims in the medical profession than any other epidemic disease. The mortality among physicians in epidemics is generally high. Osler states that in a period of 25 years in Ireland, among 1230 physicians attached to institutions, 550 died of typhus. Minkine reports that out of 13 physicians working at the typhus hospitals, 12 contracted the disease, and 6 of them died. Butler, in connection with his typhus hospital unit, states that of 6 physicians, 4 contracted it and 2 died. The mortality among the Serbian physicians, in 1915, amounted to 126 out of 350, or 36 per cent. Moreover, some of these physicians were regarded as immune from previous attacks contracted before this epidemic. Friedberger, in reporting an epidemic at Schutzen in 1915, states that 24 of the doctors were attacked and 14 died, a mortality of 58 per cent; that of 332 nurses, 71 fell ill, of whom 15 died, a mortality of 21 per cent; at the same time the disease among the Russian prisoners showed only a mortality of 7.8 per cent. Why the infection with typhus has been so common and the mortality so high among physicians is not explained. There is no evidence that there is opportunity of direct infection by some means in which the virulence of the infection (as in pneumonic plague) is uniformly greater than when it is transmitted through the intermediate host—in the case of typhus, the louse, and in bubonic plague, the flea. However, infection through the conjunctiva is possible and it has been demonstrated by Durand and Giroud that it is possible to infect mice by the intranasal installation of the virus of epidemic typhus. (See also p. 936.)

Immunity.—It has generally been regarded that an immunity, usually complete, follows recovery from an attack of typhus. Such immunity may last for a long time. However that the immunity is not permanent seems evident, as a number of well-authenticated instances of second attacks, and even of third attacks, have been recorded.

Zinsser and Batchelder found that the serum of convalescent guinea pigs contains protective bodies which protect other guinea pigs from infection with typhus virus, provided the serum is collected from the first to the fourteenth day after defervescence. Serum taken later than the 21st day no longer protected. Also, in human beings apparently protective bodies are not present in the blood after about three weeks. Zinsser (1940) suggests, therefore, that true immunity in typhus depends upon tissue resistance rather than upon circulating antibodies. With tissue cultures of rickettsiae, he has shown that convalescent sera may

develop active rickettsial agglutinins which are diagnostically reliable. Using murine organisms washed out of the peritoneal cavities of x-rayed rats and the Weigl louse vaccines (of epidemic typhus), he showed that there were cross reactions between these two organisms which indicated that they were not identical but closely related. It has also been demonstrated that phagocytosis enhancing properties (opsonins) also may develop in convalescent typhus serums and may persist longer than other immune bodies.

Epstein, using emulsions of infected lice, human convalescent serum and citrated blood, showed that rickettsiae may be actively taken up by the leucocytes.

Castenada (1936) demonstrated that opsonic substances may remain in the serum of convalescent guinea pigs for as long as 3 months after infection. It is the acquired immunity of convalescençe and the immune substances which have developed during convalescence and in inoculated animals that have encouraged the hope that methods for active immunization against the disease might be devised.

TREATMENT AND PROPHYLAXIS

Treatment.—There is no specific treatment and there is no disease in which careful nursing is so important. Shattuck, from his experience in the Serbian epidemic, emphasizes that it is certain that filth, famine, overcrowding, and lack of ventilation favor the spread of typhus. They favor it not only by increasing opportunity for transmission of infection, but also by weakening in advance the resistance of the person infected. It seems certain that bad conditions of living tend to lower the resistance of the individual and to increase morbidity as well as mortality in an epidemic of typhus.

The first fundamental principle of treatment rests on these facts. It demands maintenance of the patient's remaining strength by every possible means (1) by removal from unsanitary surroundings, (2) by good nursing, and (3) by a well regulated diet.

It is very necessary to maintain the recumbent position. Continuous rest in bed, with abundant nourishment, are important to the strength of the patient. An abundance of water should be given and the diet should consist of milk, broths, and soft solids. The tendency to skin gangrene requires constant watching.

The care of the mouth is very important. A mouth wash of equal parts of boric acid solution, glycerine and lemon juice should be used to swab out the mouth several times daily. Constipation should be controlled by enemata. It is best to give the patient abundance of fresh air, so that tent treatment with appropriate climatic environment is to be recommended. Cool sponging lessens the nervous manifestations as well as lowers the temperature. Ice bags to the head are advisable for the relief of headache. Veronal or chloral may be needed to control the insomnia and hyoscine in cases with acute delirium, with or without morphia, is of advantage in giving rest and in conserving the strength

of the patient. Cardiac stimulants are often indicated, as caffein and camphor, or tincture of digitalis. Caffeine in 0.2–0.5 grm. doses is sometimes recommended in the cases which collapse. Thyroid extract has been of value. Shattuck, in cases with collapse symptoms, found that salt solution administered intravenously to patients in which circulatory disturbances seemed to be mainly due to vascular relaxation responded satisfactorily. When patients are rapidly losing strength because they cannot assimilate food, he advocates the use of alcohol, not in small doses but freely. Lumbar puncture for the relief of the delirium and other cerebral symptoms has sometimes been of benefit. Codein is indicated when the cough is troublesome.

Menk (1942) reports that sulfapyridine has been used in the treatment of typhus in Warsaw since early 1940, especially in relation to the complications of which the most common and dangerous is pneumonia, due to secondary bacterial invasion. The impression has been gained that the drug tends to prevent pneumonia but there is no evidence that the sulfonamides influence the typhus disease itself.*

On different occasions, the serum of convalescents from typhus has been employed by many workers for the treatment of the disease. Durand (1932), Elman (1934), and others reported some beneficial results. However, Levaditi and Lepine (1938) have found that given during the course of the illness it neither arrests the evolution of the disease nor diminishes its gravity. Asheshov, in Russia, found that while it might mitigate the severity of the symptoms it did not shorten the course of the disease. Other observers, however, have recommended serum for passive immunization.

Nicolle and others have recommended for treatment, the sera of horses or asses intravenously injected with increasing doses of infected tissues. However, the majority of clinicians have abandoned the use of such sera for treatment. More recently, Zinsser and Castenada have prepared an anti-murine horse serum which they report possesses specific protective prophylactic and therapeutic action for guinea pigs. Zinsser (1940) reports that this serum has since been extensively used in Mexico, Tunis and Rumania, but with results that can be appraised only in a preliminary manner. In Mexico, where the majority of the cases, and perhaps all of them, are infected with a murine virus, the serum has given encouraging results. In Tunis and in Rumania so far there has been no indication of any degree of usefulness. Zinsser found that this serum gave only partial protection to guinea pigs which were subsequently inoculated with the epidemic European virus.

Preventive Measures.—During an *epidemic* of European typhus a plan of campaign should be made and should include: general disinfestation of people in badly infected districts; general house-to-house inspection in such districts with removal of patients to hospitals for typhus cases; disinfestation of other inmates of such houses; disinfection or disinfestation of houses from which patients were taken, or in which deaths from typhus had occurred; the establishment of quarantine and bathing and disinfesting stations at important points throughout the country; the limitation of railway travel by reducing the number of passenger trains; and the establishment of a system of limited travel permits and of inspection of travelers, only cars with wooden seats, with no upholstery being permitted to be run; provision for the cleaning and disinfecting of such cars after each journey; provision for the cleaning and disinfestation of

* Van Meerendonk (1943) has reported that one tablet of atabrine hydrochloride (0.1 gram) t.i.d. together with a daily injection of 10–20 cc. of a 20 per cent solution of calcium gluconate or a 10 per cent solution of calcium chloride is a specific treatment for typhus fever. In severe cases as much as 40 cc. of calcium chloride has proved especially effective. He emphasizes that calcium deficiency is an important factor in the disease. There has been no confirmation of the efficacy of this treatment. The use of paramino-benzoic acid has also been suggested for treatment.

public vehicles, particularly of cabs at the railway stations; the sanitary inspection of restaurants and cafes, and the establishment of regular hours of closing during the day for cleaning and disinfection, and the methods to be employed for such disinfection; regulations for hospitals in connection with the disinfestation of the wards, bedding, and linen, and of the inmates and their clothing; the establishment of free dispensaries in various cities, not only for the treatment of the sick, but for the early detection of individuals suffering with infectious disease; a campaign of education with printing and distribution of circulars regarding the nature of the disease, the manner of its spread, and the precautions to be taken to avoid infection. The details of such work obviously cannot be discussed in a textbook.

Personal prophylaxis consists especially of the destruction of body lice, or preventing their access to the person. Those attending cases should wear gowns, closely fitted at neck and wrists, and rubber gloves. Better than a gown are "unionalls," with stocking extremities to go under or over the shoes. The typhus case should be deloused with the greatest thoroughness, and his clothing sterilized.

For ridding the body of lice, the following steps are essential:

1. The hair of the body and head should be clipped.

2. The subject should be bathed, there being used freely kerosene-emulsion soap, prepared by boiling 1 part of soap in 4 parts of water, and then adding 2 parts of kerosene oil. The resultant jelly, when mixed with 4 parts of water, makes a liquid soap that is convenient to use and which may be applied effectively.

3. Following the bath, the body may be anointed with kerosene, special care being devoted to the hairy parts. Skin irritation may, however, require early removal of the oil.

4. It has been found that lice on clothing removed from the body may remain alive nine days and their eggs as long as forty days. The clothing therefore should be disinfected by one of the following methods.

(*a*) Steam; (*b*) boiling for five minutes; (*c*) 5 per cent compound cresol solution for 30 minutes; (*d*) chemicals such as cyanide or chloropicrin.

5. In the absence of facilities for carrying out the steps described, or to prevent infestation subsequently, dusting powders are sometimes used. Of these the N.C.I. powder, containing commercial naphthalene, 96 gms., creosote, 2 cc., and iodoform, 2 gms., is the most widely known; but Moore's powder—creosote, 1 cc.; sulphur, 0.5 gm., and talc, 20 gms.—is less irritating and is said to be six times as effective. It has also been recommended to wring out the underclothes in 5 per cent compound cresol solution, then drying thoroughly, or to impregnate them with substances such as the halogenated phenols. A temperature of 55° to 60°C. for 15 minutes is sufficient to kill lice and the blankets and woolen clothing may be treated in the tumbler of the laundry and thus made lice free.

Recent studies carried out by the United States Army and reported in Circular 56, Office of the Surgeon General November 1942, indicate that the best delousing of clothing and equipment can be obtained by the

use of QM issue methyl bromide, either in portable and demountable forced air circulation, gas chambers made of plywood, or in special QM issue bags made impervious by impregnation with ethyl cellulose. Clothing and equipment are not injured by this method. The fumigant, methyl bromide, is slightly more toxic than carbon tetrachloride but when used in the prescribed manner it can be safely handled and gas masks are not required by the personnel involved. The gas has great powers of penetration and when the proper dosage is used it will, in 30 minutes, destroy all insects or insect eggs, even if they are on clothing in the center of a filled barracks bag. Clothing fumigated in this way can be safely reissued to the owners within one hour, or by the time the concurrent body delousing and bathing procedures have been finished.

The approved QM issue insecticidal powder may be dusted into the seams of clothing every 7 to 10 days, not only as a delousing measure but as a prophylactic against infestation. The delousing of the body surface is carried out by barbering and by the local application of insecticides, followed by careful bathing and the combing out of any retained nits. The application of insecticides should be done 15 minutes prior to bathing by wetting the hair and skin with the following lotion:

		Per Cent
Pyrethrins		0.25
IN 930		2.0
Castor oil		2.0
Isopropyl alcohol		81.0
Water q. s.	ad.	100.0

Another satisfactory method of destroying head or crab lice is to apply to the hair and skin areas involved one of the following insecticides 24 to 48 hours prior to delousing of clothing and bathing:

Lethane 384 special, 50 per cent in mineral oil.
Lauryl thiocyanate, 25 per cent in mineral oil.
QM issue insecticidal powder.

Apply 8 c.c. of either of the above liquids to the hair and skin areas involved, or dust heavily with the insecticidal powder and rub in. Dimethyl phthalate both as a repellent and insecticide has been found to be especially effective, while D.D.T. (or Gesarol) is said to be most effective in the destruction of lice and their ova. Underwear impregnated with 1 per cent emulsion remains louse-free for a number of weeks and often after several washings (see p. 1747).

In the absence of these special preparations, the hair should be shaved or close clipped. Vinegar or 15 per cent acetic acid may be rubbed into the hairy surfaces to loosen eggs, followed by vigorous shampoo with hot soapy water containing 25 per cent kerosene and removal of any remaining nits by combing with a fine comb.

Precautions should be taken against droplet infection, as in pneumonia, and the possibility of infection occurring experimentally through the mucous membranes of the eye and nose should be borne in mind. Rickettsiae may be blown into the air in the form of dust from dried louse excreta and infection occur through inhalation especially in handling louse infected clothing. Fumigation and insecticides as lethane do not destroy rickettsiae.

Hypodermic needles used on typhus patients should be immediately carefully sterilized and any wounds about typhus patients should be carefully cauterized.

Protective Inoculation.—The field of protective inoculation against typhus is still in the experimental stage. The following methods have been particularly proposed. First the inoculation of defibrinated typhus blood, heated to 60°C. for one hour. Inoculations of this nature were made in the Turkish Army in 1915, but the results were not convincing. They were repeated on German troops in 1916, with negative results. Later Nicolle suggested active immunization by the injection of small amounts of virulent typhus blood, or typhus guinea pig serum. Such a method was not without danger and has been discontinued. Blanc has especially advocated and used a living, attenuated vaccine made by submitting to the action of ox gall the organs of guinea pigs infected with murine typhus. Blanc's vaccine has been used very extensively, and Gaud reports that more than a million people have been vaccinated in Morocco and that it has given excellent results. In Chile, however, the results appear to have been less satisfactory, where among 800 vaccinated 23 per cent were said to have showed a picture of grave typhus, and 5 died. The virus was isolated by animal inoculation from the blood of patients with vaccinial typhus by Palacios. Laurens, Fort and Bernier (1939) have reported failures in military practice from the use of this vaccine (murine living typhus virus) which they attribute to the impossibility of keeping the virulence of the vaccine constant and to its rapid loss of efficacy. Laigret has also employed an attenuated living murine virus by drying the infected brain tissues. It is reported that over 32,000 persons have been vaccinated with this murine vaccine and that there were no serious accidents. However, Laigret (1937) reports that 5 cases showed symptoms of murine typhus from 10 to 16 days after vaccinations. He reports, however, that authentic cases of typhus in those vaccinated have so far not only been very rare but have never been fatal.

Zinsser (1940) pointed out that immunization with living virus, as recommended by Laigret and Blanc, is inadvisable owing to the dangers on the one hand to the individual vaccinated and on the other to the community, with the possibility of bringing about an epidemic.

Killed Virus.—Spencer and Parker (1925) first demonstrated that immunity might be obtained in Rocky Mountain spotted fever by the use of the killed virus. Their prophylactic was prepared with suspensions of the viscera of infected ticks, ground in a mortar and killed with 0.5 per cent phenol. A single tick sometimes contained as much as 1000 infectious doses. With this vaccine, guinea pigs and monkeys can be protected against subsequent infection. (See Rocky Mountain spotted fever, p. 970.)

Weigl conceived the idea of preparing a prophylactic against the epidemic typhus virus by infecting lice with the rickettsiae through the rectum. The lice so injected died between the 9th and 12th days, when the cells lining the intestinal tract were found filled with rickettsiae.

The prophylactic was then made from carbolized suspensions of the infected intestines of the lice. The preparation of the vaccine is laborious and the inoculated lice must be fed for over a week on immune individuals before they yield an adequate harvest of rickettsiae. The immunization of a single individual may require material obtained from 50 to 100 lice. For this reason the method cannot be employed for prophylaxis on a large scale. Weigl's statistics in Poland on its use are not convincing. However, Rutten (1936) has employed the louse vaccine in protection of missionaries in Central China and believes that they have diminished morbidity and eliminated mortality and have rendered the cases in which typhus subsequently occurred milder and of shorter duration.

Zinsser and his associates first prepared a prophylactic by injecting murine virus intraperitoneally into rats that had previously been irradiated with x-rays. By this manner toxic suspensions of rickettsiae could be obtained from the peritoneal cavities and when such suspenions were formalinized it was found that guinea pigs could be completely protected by them. Casco (1932) inoculated 11 volunteers with this prophylactic and subsequently inoculated them with infectious material. Only 3 of the 11 developed typical typhus, as did 2 of the 3 non-vaccinated controls. Other results of value have been reported from Mexico.

Since the murine vaccine, however, protects only partially against the classical epidemic European infection, it is not possible to prepare a satisfactory prophylactic for epidemic typhus in rats. For this reason, Zinsser made efforts to obtain cultivations of *Rickettsia prowazeki* in large amounts. This he has been able to do by his so-called agar tissue culture method. This method, developed in conjunction with Fitzpatrick and Wei (1939) depends on furnishing a back log of isotonic agar partially buffered and adjusted by the addition of Tyrode's solution and serum, either of horse or beef, or of any other species appropriate for the work at hand. When living bits of infected tissue are laid upon this agar, diffusion into the medium, supplies conditions for the removal of metabolic products and for the supply of necessary materials for the maintenance of the cells. Zinsser (1940) reported that this vaccine was being employed in China, in Mexico, and in South America, and was also being studied in Morocco.

Cox (1938) has also prepared a prophylactic by inoculation of fertile hens eggs and injecting the virus directly into the yolk sac, the virus being subsequently killed with phenol and formalin. This method has proved to be most satisfactory for the cultivation of rickettsiae in large amounts.

The method finally employed by Zinsser, Plotz and Enders to secure large nunbers of rickettsiae consisted in a combination of the agar method—using considerably enlarged surfaces for cultivation—and the egg technique as a source of inoculum. Specifically, the minced embryonic tissue or macerated yolk sac taken from eggs on the fourth day following infection is used to inoculate large quantities of normal minced chick tissue from 10-day embryos. The tissue thus infected is distributed in large amounts on the agar surfaces of modified Kolle flasks. After 6 or 7 days' incubation at 37°C., cultures very rich in rickettsiae are obtained. They emphasize the fact that considerable quantities of tissue may be employed. Transplants can then be made by using the culture rickettsiae or new cultures inaugurated with material from infected eggs. None of these vaccines have been tried sufficiently in an epidemic of typhus fever.

However, the annual report of the International Health Division of The Rockefeller Foundation reports that five physicians that had received inoculations, particularly of the yolk sac vaccine, all later contracted the disease although the infections were mild. Fifteen cases of laboratory infection after protective inoculation with Weigl's vaccine have occurred at the German Military Institute Cracow. Further improvements in the preparation and concentration of the Cox typhus vaccine, made especially at the National Institute under Dr. Dyer and by Cragie, Plotz and others, can not now be discussed for military reasons. Circular 56, Office of the Surgeon General, United States Army, November 1942, with reference to vaccination states: A vaccine prepared with killed rickettsiae has been provided. At present this vaccine is administered by giving 3 injections of 1 c.c. each, subcutaneously, at approximately weekly intervals.

A stimulating dose of 1 c.c. should be administered every 4 to 6 months as long as serious danger of infection exists. Additional injections may be given whenever, in the opinion of the Surgeon, this is deemed advisable.

A German report by Ding (1943) states that groups of persons, (prisoners or other individuals not stated) were inoculated with one or other of six vaccines. (1) louse-gut vaccine (Weigl); (2) Cox vaccine made at Koch Institute, Berlin; (3) and (4) weaker preparations of egg-yolk vaccine made at Marburg and containing murine as well as epidemic rickettsiae; (5) rabbit-lung vaccine made in Paris (Giroud); (6) dog-lung vaccine from Rumania (Combiescu). There were also two control groups who received no vaccine. All groups were then inoculated with typhus rickettsiae six to eight weeks after they had been vaccinated. The weaker egg vaccines were said to be less effective than the others but essentially there was no difference between the results obtained with the louse, egg, and rabbit-lung vaccines, and there was no evidence that vaccination had any influence in preventing the infection. No deaths occurred in those that had been vaccinated except those with the Marburg vaccine but the fatality rates in the two control groups were 33 and 20 per cent. The incidence of the disease was unaffected by the vaccinations, but its severity was much reduced. The amount of rickettsiae introduced for the test must have beën large since the incubation periods in many cases were only 2–3 days in the control cases and not much longer in those which had been vaccinated.

Endemic Typhus (Murine Typhus), Brill's Disease

Murine typhus is widely distributed throughout many parts of the world. It has been shown recently to exist in the United States, Chile and Peru, Syria, Greece, Africa, Manchuria, Malaya, China, Indo-China, and probably the Philippine Islands.

Brill's Disease.—The distinction between an endemic form of typhus in the United States and the epidemic European typhus was first pointed out by Brill (1898). He recognized in New York the presence of an acute infectious febrile disease of unknown origin which resembled typhoid but gave a negative Widal reaction. There was intense prostration and an extensive erythematous maculo-papular eruption. After about 2 weeks, the fever abruptly ceased, often by crisis. He later (1910–11) demonstrated the similarity of this endemic infection to typhus fever, but showed that it was milder in character. For many years the condition in the United States has been known as Brill's disease. Brill noted that the epidemiology of this disease differed considerably from that of epidemics of typhus. The cases occurred sporadically, without traceable connection with one another, and no localized outbreaks occurred. Also their seasonal distribution differed from that of typhus. These factors led him to the idea that some other vector than the louse might be concerned in transmission. Anderson and Goldberger (1912) subsequently proved experimentally that Brill's disease is actually a form of typhus fever. The discoveries by Maxcy of endemic typhus in the southern states, to be presently referred to, also further elucidated our knowledge of Brill's disease.

Zinsser has studied detailed records of 538 cases of Brill's disease observed in New York and Boston between 1910 and 1933. Of these, approximately 95 per cent occurred in foreign born individuals who migrated from Russia. Ninety-seven per cent of all the cases from 1910 to 1920 were in Jews. Over 80 per cent came from Russia alone. He believes that the cases of Brill's disease represent recrudescences of infections acquired at home. In most instances cases of Brill's disease correspond epidemiologically with those of endemic typhus in the southern states.

Endemic Typhus in the United States.—The discovery of endemic murine typhus in the United States has been especially due to the epidemiological work of Maxcy (1926) in the southern United States. Like Brill in New York, he was unable to explain satisfactorily the nature of the disease and its spread and its seasonal incidence on the assumption that the louse was the vector. The large number of cases which occurred among persons handling food stuffs inclined him to the belief that rats and

mice might be the reservoir and that the disease was transmitted to man by fleas, mites or ticks.

Dyer, Rumreich and Badger (1931) and other workers of the United States Public Health Service, next demonstrated the presence of the virus in rat fleas taken from rats caught in Baltimore. Mooser, Castenada and Zinsser then found the virus of tabardillo in the brain of Mexican rats, and Dyer, Rumreich and Badger (1931) demonstrated experimentally the flea as a vector. In a short time the distribution of typhus virus in rats was demonstrated in many countries as a wide-spread infection. This murine type has been especially found where opportunities for louse

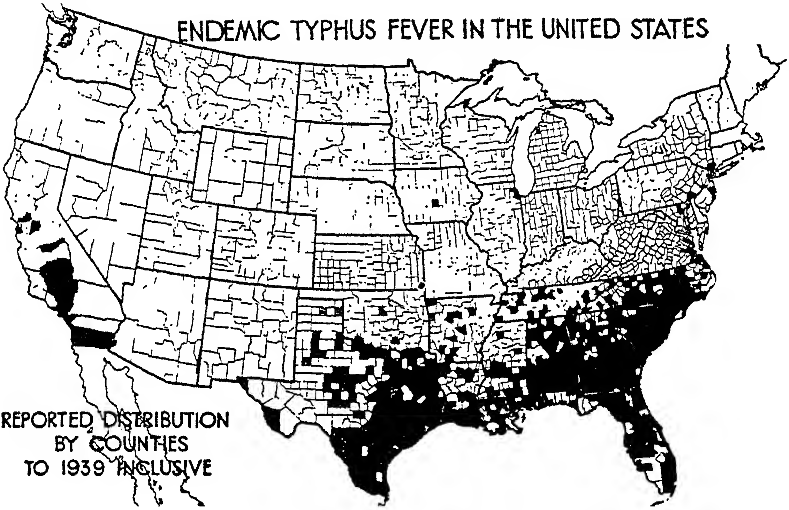

FIG. 216.—From article by Dr R. E. Dyer. Courtesy Am. Jour. of Tropical Medicine.

transmission are not great, but it has also been found in centers where epidemic typhus also exists, as in Moscow, Leningrad and Istanbul. Brill's disease has also been reported in Palestine; in 1927 there were 85 cases, with but one death. This mild form of typhus has also been encountered in Australia and in North and South Africa. Zinsser and several other investigators have shown that murine typhus may also pass from man to man by the louse, as well as by the tropical rat flea (*Xenopsylla cheopis*). The extension of endemic typhus in the southern United States is due particularly to the migrations of the brown rat *Rattus norvegicus* and of the tropical rat flea.

ETIOLOGY

The Virus.—The close relationship between the viruses of classical epidemic typhus (*Rickettsia prowazeki*) and of those of the endemic murine typhus (*R. mooseri*, or *R. prowazeki* var. *mooseri*) is seen in the agglutinins of the Weil-Felix reaction of strains OX19 and OX2 of *B. proteus*, but not against strain OXK in each type of infection. Considerable but incomplete cross immunity exists between these infections.

They, moreover, may be distinguished by the fact that the murine endemic virus in male guinea pigs induces fever accompanied by a characteristic reaction in the tunica vaginalis, with rich production of rickettsiae (the Neil-Mooser reaction). With the virus of classical epidemic typhus, these animals usually suffer only a slight rise of temperature, or the infection may remain inapparent and the scrotal reaction is absent unless the resistance of the animals is artificially lowered, as by a vitamin deficient diet. Also, in rats the murine endemic virus produces fever, sometimes scrotal reactions, and after resistance is lowered by irradiations with X-rays, rich peritoneal accumulations of rickettsiae occur. On the other hand the classical epidemic typhus virus gives rise in rats only to inapparent infections, or rarely short fever during which the virus multiplies without causing symptoms and then dies out. Rich accumulations of rickettsiae are not obtained in irradiated rats.

Transmission.—The virus of endemic typhus is kept alive in nature in rats, and is transmitted from rat to rat and from rat to man by rat fleas, *Xenopsylla astia* and *X. cheopis* (Mooser and Dyer, 1931). It thus is similar to plague in its epidemiology. The rat louse (*Polyplax spinulosus*), as well as the flea, transmitts the disease from rat to rat (Mooser, Castenada and Zinsser, 1931), but the rat louse does not bite man. Possibly the tropical rat mite, *Liponyssus bacoti*, may also transmit the infection in rodents (Dore and Shelmire, 1931). Infection in man is probably introduced by scratching or rubbing the faeces of the flea into the skin, but not directly by the bite. The rickettsiae multiply greatly in the flea, so that after about a month one flea may contain enough organisms to infect a very large number of guinea pigs. In other instances, the number of rickettsia in the flea may be small in comparison with those in the louse.

Rickettsial infections of lice, including *Pediculus humanus* and *Polyplax spinulosus*, the rat louse, which is an important transmitting agent from rat to rat, are regularly fatal to the louse within 2 weeks, whereas the rat flea, *Xenopsylla cheopis*, apparently is not harmed by the infection and may remain alive and infectious for several months.

As noted, the murine typhus virus produces a severer reaction when injected into the peritoneal cavity of rats and guinea pigs than does the classical epidemic European strain. In the former, the exudate in the tunica vaginalis contains many rickettsiae and the scrotal sac is considerably swollen. Wolbach (1940) states that this should be called the "tunica reaction," to distinguish it from the scrotal swelling occasioned by the inoculation of guinea pigs with Rocky Mountain spotted fever virus. In Rocky Mountain spotted fever, he regards the scrotal swelling as due to thrombosis of the blood vessels of the scrotal sac wall.

In addition to the transmission of the disease by arthropoda, fleas and lice, there is considerable evidence of the transmission of murine typhus to animals by way of the alimentary tract (Blanc, 1937, Violle, 1938, Wolbach, 1940). Dyer has demonstrated that the faeces of infected fleas in the United States contain rickettsiae, and Brumpt (1932) has

confirmed this in Europe. Nicolle failed to transmit epidemic (classical) typhus to rats by feeding infected lice on them, but Nicolle (1934) and Lechuiton (1938) found that the *Rickettsia* of murine typhus is present in the urine of infected rats and they believe the virus may be transmitted to man by the ingestion of food contaminated with rat urine. One of the larger triatomata may become infected with *Rickettsia* when fed on infected rats. The triatoma does not convey the disease to other rats by biting, but rats may become infected when they ingest such triatomata. The virus of murine typhus may persist for long periods in the brain of rats. Zinsser has shown that the murine virus will survive indefinitely in mouse passage, whereas the European attenuates in these animals and cannot be carried beyond the third or fourth generation. The murine type is more virulent for rats than the European.

Sparrow and Lumbroso also showed that murine virus was capable of infecting guinea pigs when instilled into the nose, or placed on the conjunctiva. Castenada (1939) also found that intra-nasal instillation of murine virus into etherized rats or mice produced a pneumonia characterized by considerable development of rickettsiae.

EPIDEMIOLOGY OF ENDEMIC TYPHUS

Geographical Distribution and Prevalence.—According to laboratory investigations, the virus of the typhus of Mexico (tabardillo), although producing an epidemic disease which is louse borne, corresponds to the virus of the murine type. Elsewhere the murine type is endemic mostly in warm climates, where opportunities for louse transmission are not great. It has been encountered in the southeastern United States, South America, Manchuria, Malaya, Syria, Greece, Africa, China, Indo-China, and the Philippines. In the United States, about 90 per cent of the reported cases have been in Alabama, Georgia and Texas. In Alabama, an average of 60 to 80 cases have been recognized each year, with the disease confined almost exclusively to the southern and southeastern part of the state, in which regions heavy rat infestation has been encountered. The disease still persists in these regions, 342 cases being reported in 1938. Bowdoin and Boston (1940) have analyzed 4762 cases which have occurred in the state of Georgia from 1932 to 1938. In this state, the number of cases was seven times greater in the white race than in the negro race. Nearly one half of the cases in the United States occur in Georgia. Musser (1940) reports 115 cases in the State of Louisiana and points out that the disease is increasing there.

Dyer (1941) has shown that there has been an almost continual increase in the number of cases in the southern states since 1929, though there was a slight decrease in 1934 and 1935 following extensive rat-proofing campaigns in Georgia, Alabama and Texas. There was also a slight apparent recession of cases in 1938, followed by an increase in 1939. Fig. 216 which he has prepared shows the present distribution of the disease in the United States. As late as 1932, the northern limit of it in Alabama was about on the line with Montgomery. Since that time, cases have

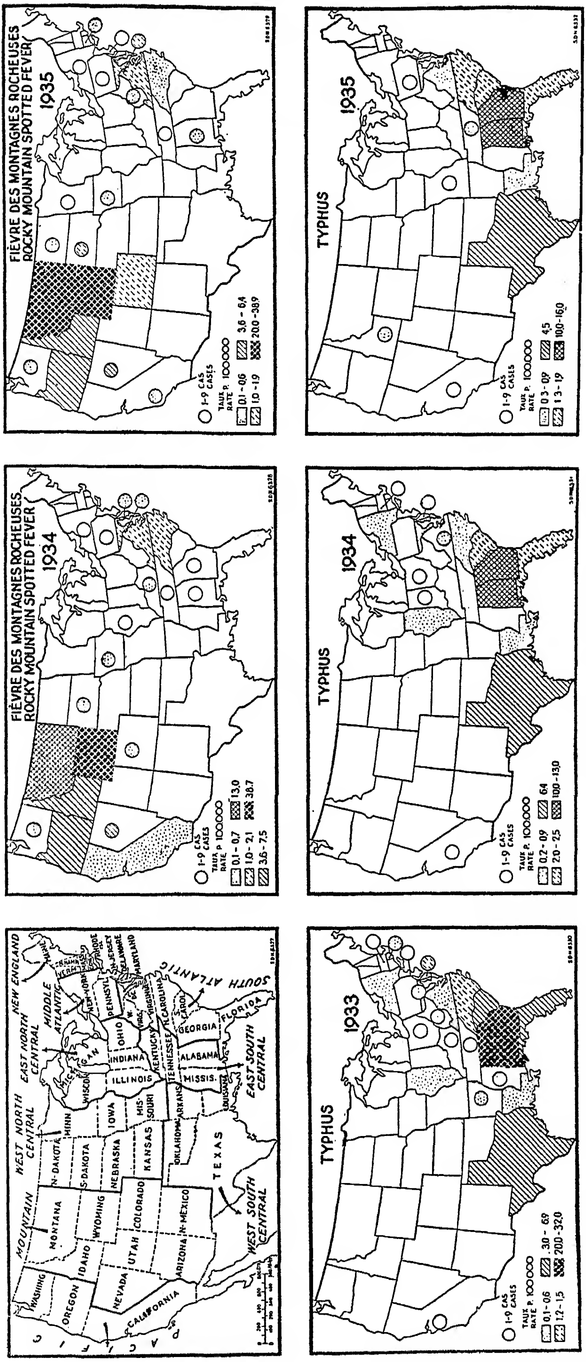

FIG. 217.—Distribution of tick-borne spotted fever and of flea-borne endemic typhus in the United States of America. (Epidemiological Intelligence Service of the League of Nations.)

appeared further north in that state, and at present the known northern limit of typhus in this section has reached central Tennessee. Meleney (1941) reports 75 cases in Nashville.* The factors which control the geographical spread of endemic typhus are not entirely clear, though the common gray rat is regarded as the most important factor and the distribution of the rat flea, *Xenopsylla cheopis*, which is apparently the most efficient vector is likewise important. Dyer (1944) reports transmission to man most probably occurs through the medium of the infected feces of rat fleas.

The seasonal occurrence of the disease has remained constant, the majority of the cases occurring in the summer and fall. The increased incidence of the disease in Alabama has not been accompanied by an increasing mortality. The fatality rate there has varied greatly with age, being less than 2 per cent for persons less than 45 years, 5 to 7 per cent for the ages 45 to 64 years, and approximately 30 per cent for persons more than 65 years.

Maxcy's investigations have shown that the incidence of the disease is twice as high in the male as in the female, that the negro appears to be very much less susceptible than the white, but that the disease does not prevail in any special strata of society.

The maximum occurrence of the disease is in the summer and fall, in direct contrast to the prevalence of epidemic European typhus in the winter and spring months. Also, the case fatality rate is low, with a small proportion of deaths in the lower age groups.

Some confusion regarding the transmission of murine typhus in the United States was occasioned by the fact that cases of Rocky Mountain spotted fever occurred at the same time in the same states, the latter, however, being a tick borne disease.

In regard to the virus of Brill's disease, Zinsser (1934), after a study of cases in Boston and New York, has come to regard Brill's disease as an imported form of the classical European typhus which has become established in America in endemic form and distinct from the endemic typhus of the southern United States and from the tabardillo of Mexico. He reports that the virus of Brill's disease behaves in laboratory infections of animals like the European type. He believes that the cases represent recrudescences of old infections originally acquired in Europe and that such cases may serve to maintain epidemic prevalence. According to this view, we must consider that in our eastern seaports and in the southern states there are 2 coexisting forms of endemic typhus, one known as Brill's disease and the other as endemic murine typhus. In addition, cases of Rocky Mountain spotted fever may also be present. Recent reports show that endemic murine typhus is increasing in the southern states, while the existence of Brill's disease is said to be steadily decreasing.

CLINICAL FEATURES

The clinical course of *endemic typhus* is in general similar to that of the epidemic disease, except that the symptoms are comparatively mild, complications are rare, and the mortality low. In the United States, according to Dyer (1941) the mortality is less than 1 per cent and most of

* Dyer (1944) points out additional foci have occurred in Cleveland and Cincinnati and in Washington, D. C.

the deaths are in patients over 50 years of age. Gordon (1940) points out, however, that the physician with ordinary experience will not always find the distinction between endemic typhus and Rocky Mountain spotted fever simple. The incubation period is from 6 to 14 days in endemic typhus. The fever generally lasts about 2 weeks, and the temperature is usually normal by the 16th day.

Rumreich (1933) points out that the disease may either begin abruptly, either with a chill or chilliness, with slight fever, or start gradually with irregular development of the symptoms, the temperature rising progressively day by day, reaching 102° to 105°F. in 3 to 6 days and lasting about 14 days, to fall by rapid lysis.

The rash, the most characteristic finding, appears as in epidemic typhus, about the fifth day, usually on the chest and abdomen and medial surface of the arms. It may not extend further, or it may spread and involve the whole body; the feet, palms and soles usually being excepted. In character, it consists of rose or dark red macules fading into the surrounding areas. The macules do not disappear on pressure. Though similar to that of epidemic types, it is usually less extensive and petechiae are less common. Extensive skin necroses have not been reported. The rash lasts from 2 to 10 days, when it rapidly disappears.

The mental condition is much less altered than in epidemic European typhus, and the delirium of the latter is almost wholly lacking.

The diagnosis and treatment of endemic typhus has already been discussed under epidemic typhus. Since the disease is usually so much milder, but little treatment is often required.

PREVENTION

Since endemic typhus is similar to plague in its epidemiology, satisfactory rat-proofing is undoubtedly an important means of prevention. Rat extermination campaigns through poison and trapping are also of value.

Bowdoin and Boston (1940) have reported that rat-proofing was the only permanent method of control in the state of Georgia. Educational campaigns in rat control measures may be of value.

Prophylactic inoculation for epidemic typhus has already been considered, p. 951. Dyer (1941) has considered the use of a vaccine to control endemic typhus, but in his opinion this may be dismissed from consideration, since cases of endemic, typhus in the United States are relatively few in number and their occurrence is sporadic. To effect any demonstrable decrease in the number of cases would require vaccination on a scale that is not warranted in the light of our lack of knowledge of the preventive value of our present vaccines. Also, a vaccination program against endemic typhus could only be expected to prevent typhus in the vaccinated individual and would have no effect in reducing the exposure to infection of other individuals, since an animal other than man is the reservoir of the infection.

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Chapter XXVI

SPOTTED FEVER OF THE ROCKY MOUNTAINS

Definition and Synonyms

Synonyms.—Rocky Mountain fever. Tick fever of the Rocky Mountains. Black fever. Blue disease.

Definition.—An acute, specific, infectious, rickettsial disease transmitted by ticks. It is characterized clinically by an onset with a chill and continuous, moderately high fever terminating in lysis; severe arthritic and muscular pains; and a profuse macular eruption on the skin, later becoming petechial, and appearing first on the ankles, wrists, and back, but rapidly spreading to all parts of the body.

History and Geographical Distribution

History.—The disease was first noted in the Snake River Valley of Idaho about 1893 and in the Bitter Root Valley of Montana about 1890. There is some evidence that the disease may have existed among the Indians prior to the advent of white settlers in the Bitter Root Valley. It is interesting to note that the first white settlers of the Bitter Root Valley suffered from what was considered a very fatal form of "black measles."

The disease was observed by Dr. M. W. Wood, U. S. A., in 1896, and by Maxcy in 1899. For many years it was supposed to be confined to the northwest mountainous regions of the United States, especially Idaho and Montana, with occasional cases in Wyoming, Utah, Nevada and California. However, in 1930, in connection with the study of endemic typhus in the United States, the Public Health Service established the fact of its existence in the Allegheny region and it has now been reported from almost all of the states.

In 1902 Wilson and Chowning reported that the disease was transmitted to man by the bite of the tick (*Dermacentor andersoni*). At that time they thought the infection was due to a piroplasma. Later Ashburn and others, while accepting the tick transmission, failed to corroborate the piroplasm as the etiological factor.

It is chiefly to Ricketts that we owe much of our detailed knowledge of the transmission and epidemiology of the disease. The work of McClintic and Frick along lines of prophylaxis has given us practical measures for its control, and Ricketts, Wolbach and Frick have also made valuable observations regarding the etiology of the disease.

Geographical Distribution.—Prior to 1930 the disease was believed to be confined definitely to states west of the Mississippi River. Since that date Spencer and Maxcy (1930) and Carey and Duncan (1938) have shown that its geographical limits have been greatly extended in the central and eastern states. The more recently discovered form of Rocky Mountain spotted fever has become known as the "eastern type" of the disease, and of the eastern states, Maryland, Virginia and North Carolina have shown the greatest number of cases. In 1937, 31 states reported cases of Rocky Mountain spotted fever, several of which were contracted in Massachusetts. Of 2190 cases reported for the entire country from 1933 to 1937, 65.5 per cent occurred in the mountain and Pacific states, and 27.4 per cent were in the south Atlantic states. These two areas combined accounted for 93 per cent of the total reported cases for the entire country. In 1938, the Public Health Service reported a total of 378 cases, though it was stated that these figures were preliminary and incomplete. Hampton and Eubank (1938) point out that the number of cases of spotted fever in the eastern states has gradually increased.

Philip, in August 1939, reported that cases had occurred in all states with the exception of Kansas, Wisconsin, Michigan, Connecticut, Rhode Island, New Hampshire, Vermont and Maine.

It is now believed that the exanthematic fever of São Paulo, Brazil and fievre boutonneuse, Marseilles, as well as the tick-bite fevers of Africa, are closely related diseases and that the causative agent of each is closely related to the other, and that all may be included in the spotted fever group of the genus *Rickettsia*.

Luis, Patiño-Camargo (1941) has reported a new American focus of Rocky Mountain Spotted Fever in the interior of Colombia, South America. The first cases being identified during an epidemic in the Magdalena river basin among a rural population along the Tobia river. There were 65 cases of Spotted Fever with 62 deaths during 1934–1936. Three strains of virus were isolated and experiments were being performed to see if a cross immunity exists between the Colombian strains and the Montana Rocky Mountain Spotted Fever strain.

Etiology and Epidemiology

Etiology.—The disease is due to a species of Rickettsia, *R. rickettsi*. Rickets noted certain chromatin-staining bacteria in man and in eggs of infected ticks which were about 1μ long by 0.3μ broad, and showed chromatin staining, resembling somewhat *B. influenzae*. They appeared as two lanceolate-shaped bodies. These bodies are now recognized as belonging to the group of organisms known as the *Rickettsia*. Wolbach, who studied the disease in 1919–20, named the organism of spotted fever of the Rocky Mountains *Dermacentroxenus rickettsi*. It is now classified by most authorities in the Genus *Rickettsia*.

Rickettsia rickettsi, like other organisms of the genus, is minute, bacterium-like, and does not stain well with aqueous solutions of ordinary bacterial stains. Giemsa's stain is best for its demonstration. In man and susceptible animals it has been found constantly in the lesions of the disease. In the tick which transmits it, it undergoes a definite morphological sequence. It has not been cultivated on artificial media, but only in tissue cultures. These cultures remain virulent for laboratory animals for long periods. Tissue cultures of the organisms of Rocky Mountain spotted fever and typhus have been studied by Pinkerton. who finds

that both in cultures and in the tick, *Dermacentroxenus rickettsi* invades and multiplies within the nuclei of cells, while *Rickettsia prowazeki* grows only in the cytoplasm of the cells. The organism is transmitted in the tick from generation to generation, and hence the maintenance of the disease may be independent of human or animal passage. The virus is extremely susceptible to physical and chemical agents, although it may survive in a frozen and dessicated state for a considerable period.

Animal Susceptibility.—The disease may be transmitted to monkeys, rabbits and guinea pigs. White rats and mice are said not to be susceptible. Infected ticks have been taken from rodents in the Bitter Root Mountains and from the Rocky Mountain goat.

Ricketts reported that a reservoir of the virus was to be found in ground squirrels, chipmunks and mountain rats, and that ticks feeding on these rodents might become infected and transmit the disease to man.

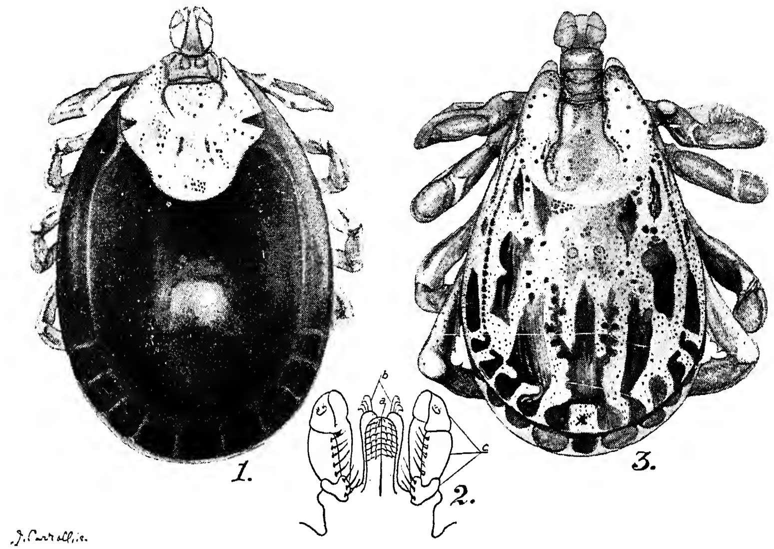

FIG. 218.—1. Female *D. andersoni*. 2. Head showing (*a*) hypostome, (*b*) chelicerae, (*c*) palps. 3. Male.

The virus can be propagated indefinitely in guinea pigs without loss of virulence by weekly inoculations into another animal.

Transmission.—Transmission of the disease in the western U. S. is by the tick *Dermacentor andersoni*, the common wood tick of that region. As the virus is transmitted to the egg, the infection can be kept up in the tick without another reservoir of virus. However, numerous animals of this area are susceptible, and undoubtedly play a part in the transmission of the disease to man, although none have been found naturally infected. Unlike epidemic typhus, man has no rôle in the transmission of this disease. In the eastern states *D. variabilis* is the natural vector. It is the common dog tick of that region. Only adult ticks commonly attack grown persons, while the larvae and nymphs infest small mammals particularly rodents.

Epidemiology.—The usual and perhaps only method of transmission in nature is through the bite of the tick. Animals cannot be infected by

contact, and no instances of contact transmission from man to man have been reported. The disease is usually one of rural communities and generally only one case is found in a house, which also indicates the improbability of contact infection, as well as the transmission of the disease by bedbugs and lice.

It is at the time when ticks are most abundant that the disease is most common and the seasonal incidence of spotted fever corresponds to the tick seasons of the locality concerned. Thus in the northwestern regions of the United States the tick (*Dermacentor andersoni*) is most prevalent from the middle of March to the middle of June and in that region the majority of the cases of spotted fever occur in April, May and June, with occasional cases in March and July and September. In the eastern states the tick, *Dermacentor variabilis* (the dog tick), appears in March and December, most of the cases occurring in June, July and August. The greatest number of cases occurs in persons engaged in outdoor occupations which take them into tick infected areas, as adult males. In the eastern states, infection of women and children is more common, perhaps because of dogs bringing ticks into the house.

Amblyomma americanum has been found naturally infected and the immature stages also attack man. Potential agents are *Dermacentor occidentalis*, the Pacific Coast tick; *Amblyomma cajenneuse*, Texas and Florida, and *Rhipicephalus sanguineus*, the brown dog-tick which is found along the Gulf coast, and *Dermacentor parumapartus* occurring on rabbits in the southern Rocky Mountain region and along the Pacific Coast. Now there is a tendency to disregard separation into the Eastern and Western types according to virulence (Topping 1941).

The age distribution of western and eastern spotted fever shows some differences, as in the east the higher percentage of cases occurs in the age group 5 to 9 years. Also, in the east the distribution is more even between the sexes. The life in the east, with vacation treks during summer, tends to bring all ages and both sexes into areas where the dog tick is prevalent.

A few instances of infection have followed crushing of the ticks and removing them from dogs. The virus is present in the blood of man during the entire febrile course of the disease.

Pathology

The cadaver sometimes shows marked jaundice, with petechial spots on extremities and trunk. There is marked venous engorgement and the blood is very dark and fluid, and clots slowly.

The pathological histology is in many respects similar to that of typhus. In the male, there is frequently extensive haemorrhage and necrosis in the tissues of the scrotum, and there may be necroses of the skin of the ears, face, fingers, toes and vulva. The spleen is usually several times the normal size. It is firm and dark red. Rickets noted especially enlargement of the lymph glands. Wolbach has especially studied the histological-pathological changes. The distinctive features are those connected with the distribution and character of the blood vessel lesions in the skin and sub-cutaneous tissues and in muscles, and in the testes and their appendages. Haemorrhages into these tissues are almost constant. The heart shows no peculiar change and the myocardium is usually normal. Changes of the lungs are not common, though occasional broncho-pneumonia may be present. The gastro-intestinal tract, pancreas, liver, adrenal glands and kidneys show no gross changes. The brain may show some injection of the blood vessels of the pia arachnoid.

Wolbach found microscopical lesions of the blood vessels in the skin and sub-cutaneous tissues taken from all parts of the body, in the testes, in the skeletal muscles, rarely in the blood vessels of the thyroid and gastro-intestinal tract. The vascular lesion at first consisted of a proliferative reaction of the endothelium, followed by necrosis with thrombus formation. The rickettsiae are found in the endothelial cells and in smooth muscle cells of the blood vessel walls. Perivascular accumulations of cells occur, though they are not so striking as in typhus. Small focal necroses may be present in the liver, as in other infectious diseases. The spleen may show extensive engorgement with blood and marked phagocytosis of red blood corpuscles. There is almost complete depletion of lymphoid cells. Wolbach did not observe lesions of the central system in the western form of the disease, either in man or in guinea pigs artificially infected. However, Lillie has reported focal brain lesions in 4 of the eastern cases which were fatal. In a subsequent report (1941) he found such lesions throughout the brain in all cases fatal after the twelfth day, but only occasionally in the earlier fatal cases. In addition to the lesions resembling those found in epidemic typhus, there were arteriola thrombo-necroses with surrounding infarctions. In the eastern cases, enlargement of the spleen is said to be less marked and the haemorrhagic lesions of the skin and serous membranes are less common than in the cases of the western type.

The pathology of Rocky Mountain spotted fever in animals such as guinea pigs, rabbits and monkeys, is similar to that observed in man.

Symptomatology

The period of incubation is from 3 to 7 days, when the disease sets in with considerable abruptness, with more or less marked rigors, headache, malaise and severe pains of the larger joints, but without inflammatory changes. In milder cases the incubation period may be as long as 14 days. However, in 2 experiments upon human beings, in which the disease was transmitted by a tick, the incubation period was 3 and 9 days. Some of the cases present a prodromal period lasting a day or so, with malaise and chilly sensations followed by the symptoms noted above. Hyper-aesthesia and photophobia are apt to be present during the course of the disease.

The eruption first appears from the second to the fifth day as rose colored macules about the wrist and ankles, thence spreading over the extremities and extending to the trunk and forehead. The rash appears later on the palms of the hands and soles of the feet and scalp. Sometimes it is present on the eyelids and the mucous membranes of the mouth and pharynx. The macules tend to become petechial.

The pulse at first is not very rapid (90–110) and the fever rises steadily day by day from the initial 102°F. to reach a maximum of about 105°F. by the end of a week or so. In very severe cases in the Bitter Root Valley, temperatures from 106–107°F. have been recorded. The fever holds during the second week, with slight morning remissions. When recovery occurs the temperature usually begins to fall at about the end of the second week, continuing by lysis so that normal temperature is reached at about the end of the third week. In fatal cases, the temperature may

drop to normal or sub-normal, only to rise shortly before death, which usually takes place between the sixth and twelfth days of the disease. The pulse is at first full and strong, but gradually loses volume and about the fifth day becomes weaker and more rapid, usually ranging from 110 to 140, or even higher before death. In milder cases, however, it may not exceed 90. The respirations are usually increased and frequently to 30 or 40 a minute or even higher before death. The lungs are usually not involved, but there may be a mild bronchial cough. A toxaemic condition appears early. A stuporous state is fairly common, but in many cases the mind is clear throughout the course.

The spleen may be palpable early in the disease and quite firm, not soft like the spleen of typhoid fever. Kidney involvement may show itself early as an albuminuria. Constipation is rather a constant feature.

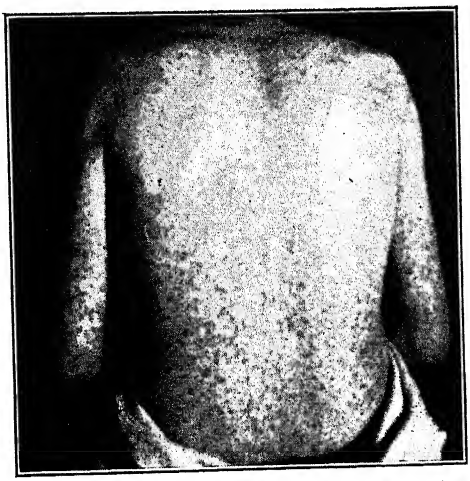

FIG. 219.—Generalized eruption of spotted fever of the Rocky Mountains. (Courtesy of Doctor Frick.)

Icterus and vomiting tend to come on later in severe cases. Gangrene of the tonsils, scrotum and prepuce are more common in reports of the milder type of the disease, as seen in Idaho, than in the more severe cases of Montana. Necroses of the fingers, toes, vulva, lobes of the ear, and mucous membrane of the soft palate may occur in the third week.

Nervous Symptoms.—In some localities restlessness and insomnia have been reported as common throughout the disease and constitute its most distressing features. Hyperesthesia may be severe. Delirium is frequent in severe cases during the height of the fever, and coma usually precedes death by a few hours or a day. Wolbach has found convulsions rare. There is occasional muscular rigidity and opisthotonus. Pneumonia, which is rare, is practically the only complication. In uncomplicated cases there is a moderate leucocytosis early in the disease, falling to about 10,000 or 12,000 after a few days. There is an increase in the

large mononuclears. The eosinophiles are decreased and may be entirely absent. The red cells are often decreased in number as the disease progresses, and may fall below 3,500,000.

Diagnosis

The disease must be distinguished especially from cerebrospinal meningitis, typhoid fever and measles, as well as from the other typhus-like diseases. Cerebrospinal meningitis generally shows more marked nervous symptoms and rigidity of the neck. There is also a much higher leucocytosis in meningitis and the blood culture or spinal fluid examination should differentiate. The macules of measles are somewhat similar, but are more dusky red and are in abundance on the face, and Koplik's spots are present. Then, too, the coryza of measles is absent.

More sudden onset, joint pains, and negative Widal reaction differentiate it from typhoid fever. The differentiation of Rocky Mountain spotted fever may be made especially by the inoculation of the guinea pig. The guinea pig, while susceptible to both typhus and spotted fever is more easily infected with the latter, and in typhus fever usually shows only a febrile reaction, while in spotted fever there is generally an enlarged spleen and scrotal swelling and necrosis. Nevertheless the strains of spotted fever virus isolated from various parts of the United States and South America differ in the reaction which they produce in the guinea pig. Wolbach has found that typical western spotted fever virus regularly causes dry necroses of the scrotum, a cause of the severity of the vascular lesions, while eastern spotted fever only rarely produces conspicuous lesions of the scrotum. Occasionally it has produced infiltration of the tunica vaginalis similar to that of epidemic typhus. Pinkerton has reported that a strain isolated by Reimann from a case in Minnesota and one by Monteiro in a case in São Paulo produced involvement of the tunica vaginalis in guinea pigs, with considerable regularity. The eastern strain of spotted fever of Rumreich is said to produce focal lesions in the brain of guinea pigs, while typical western strains and the Minnesota strain did not. These confusing factors with different strains are not yet entirely explained. They have suggested to some authors the occurrence of strains intermediate between typhus and spotted fever. Wolbach believes, however, that the morphology and grouping of the intracellular parasites found in the scrotal sac is sufficient for diagnosis in the hands of one who is familiar with epidemic typhus and spotted fever virus. In tissue cultures, the organisms of spotted fever invade the nuclei of the cells, while typhus rickettsiae invade only the cytoplasm. Differentiation can also be made in laboratory animals by cross immunity tests, since neither disease confers immunity against the other.

The geographical distribution of the disease and the association of the tick bite may also be of value in diagnosis. In fièvre boutonneuse and tsutsugamushi disease there is a local lesion present, while in the latter disease the virus in immunologically distinct from either the Rocky Mountain spotted fever group or the typhus group (see p. 946).

A positive specific Rickettsia complement fixation test may be obtained and is usually present about the 10th day and may persist for years after convalescence. This test serves to differentiate the disease from either epidemic or endemic typhus. Plotz Reagan and Wertman (1944) have found the test of particular value in separating it from other forms of rickettsial disease.

Prognosis

The mortality of the disease has varied considerably in certain localities. For the whole United States it has been given as about 23%. It is somewhat remarkable that the mortality in western Montana has been reported rather constantly as approximating 75–90 per cent, and in Idaho not over 5 per cent. More recent reports state that in western Montana it is about 15 per cent. In the past few years there have been fewer cases in Idaho, but the mortality has increased to about 25 per cent. In the eastern states from 1933 to 1936, 465 cases occurred in the South Atlantic states, in which the mortality was 18.1 per cent. In the same period, for 1230 cases in the mountain and Pacific states, it was 19.4 per cent (Hampton and Eubank, 1938). The Public Health Service has suggested that the mortality has been greatly reduced in recent years in some areas of the Rocky Mountain region by vaccination. This, however, does not explain the differences in mortality in earlier years. In Brazil, the mortality of Sao Paulo disease has been in the neighborhood of 80 per cent.

Where the nervous manifestations are marked, the prognosis is more unfavorable. Death tends to occur in the second week and patients living through this week have a good chance for recovery. The death rate is greatest in old people and least in young children.

Prophylaxis and Treatment

Prophylaxis.—The general measures for the control of the disease in the Bitter Root Valley have been directed especially toward the reduction of numbers and the elimination of the distribution of ticks. Some success has been obtained there in the destruction of the small mammals which act as hosts of the larvae and nymphs, and also the dipping of cattle which are infested with adult nymphs. Clearance and cultivation of the land in some areas has rendered the locality comparatively safe against infection. In most regions, however, where clearing and cultivation of the land cannot be carried out, prevention of the disease by the control of tick carriers has not proved practicable.

Brumpt has suggested the introduction in the United States and acclimatization of hymenopterous insects (*Ixodiphagus*) which are parasitic upon and destructive to various genera of ticks. So far at least, some of the attempts have proved unsatisfactory.

Personal prophylaxis depends upon avoidance of tick bites. If one has to visit tick infested regions, protective clothing should be worn—high boots, leggings, puttees, and heavy socks worn over trouser legs—should be employed, as ticks will crawl up the outside of clothing. Careful inspection should be made of the body daily, and particularly the back of the neck, as well as inside the clothing. *Dermacentor andersoni* usually requires a long time to become attached and feed on the human host—at least one or more hours—hence inspection of one's person for ticks after returning from exposure and removing those found would tend to prevent infection.

When these ticks attach themselves to the wool of grazing sheep, 87 per cent seem to die, possibly from the effect of the fat in the wool. Again such sheep can be dipped for further destruction of the ticks.

There is no satisfactory repellant which can be placed either on the clothing or on the body to prevent tick attachment.

Protective Inoculation.—Spencer and Parker (1935) have used a phenol-formalized emulsion of ground-up infected ticks (*Dermacentor andersoni*) against Rocky Mountain spotted fever. The inoculation is said to produce as a rule only slight local symptoms, although occasionally there may be headache, some fever, and general malaise for 24 to 48 hours. Rarely there may be an urticarial rash, but such cases usually clear up without serious consequences. Parker has reported that only 64 out of 15,000 vaccinated in an endemic area developed spotted fever. Protection was complete against the mild Idaho virus, the morbidity falling among the highly exposed shepherds from 6 per cent in the unvaccinated to 0.5 per cent in the vaccinated, while against the highly virulent Bitter Root Valley virus of Montana, protection was shown by a fall in fatality from 82 per cent among the unvaccinated to 6.6 per cent among the vaccinated. Similar protection was given to laboratory workers handling the Bitter Root virus; infection occurred in 22 cases, and of 7 not vaccinated all were fatal, whereas among 15 vaccinated only 1 died. Since 1940 the vaccine has been prepared from the chick embryo by the yolk sac method of Cox. For active immunization the National Institute of Health recommends either three 1 cc. injections or two 2 cc. injections given subcutaneously at 7 day intervals.

Montiero (1933) showed that with the South American tick, *Amblyomma cajennense*, a similar vaccine could be prepared, effective in guinea pigs, against North American spotted fever and São Paulo tick typhus, and Canet (1934) also produced a spotted fever vaccine using the European tick, *Dermacentor reticulatus*.

Gordon (1940) points out that the protective value of this prophylaxis is definite, but the degree and duration of protection varies with individuals and with the virulence of the infecting strain. While children may be fully protected against the usual fatal form of spotted fever, adults are only occasionally protected.

Parker (1941) has reported the results of 15 years of prophylactic vaccination and finds the vaccine has definite immunizing value. The average vaccinated person maintains for somewhat less than a year an immunity of sufficient degree to afford protection against relatively mild strains. Parker thinks immunization each year is the only safe procedure.

Treatment.—A hyperimmune rabbit serum has been elaborated by Topping and is recommended by him for treatment. The studies of Topping and of Pinkerton (1944) show that the sulfonamides are ineffective and possibly detrimental from experiments performed on laboratory animals. In general, treatment should be symptomatic. Just as with typhus fever, the most important point in the care of the patient is good nursing. The room should be darkened and quiet maintained. Cool sponging lowers the temperature and is a tonic for the nervous disorders. An ice cap is often of value for the headache. The diet should be liquid and water should be given freely on account of the tendency to renal involvement. There is a tendency to heart failure, so that the recumbent position is demanded and cardiac stimulants indicated. Further indications for treatment are given under the description of typhus fever on p. 948.

Wolbach (1937) suggests that on theoretical grounds the transfusion of blood from an immune donor should be tried when opportunity occurs in the early stages of the disease.

Spotted Fever Group

TICK TYPHUS, TICK BITE FEVER, FIÈVRE BOUTONNEUSE

The rickettsial diseases of man transmitted by the family of ticks *Ixodidae* are now known to be of wide geographical distribution, and include fièvre boutonneuse (Marseilles fever), escarro-nodulaire of the Mediterranean countries, and tick bite fever of South Africa, Kenya, India, and South America. There is evidence that these diseases are closely related to one another and to the Rocky Mountain spotted fever of North America. Fièvre boutonneuse was first described by Connor and Bruch in 1910 in Tunis. Subsequently different French and Italian observers reported the existence of a disease in the Mediterranean regions and in Marseilles and among other districts in southern France, as well as in Italy, Portugual, Spain, Greece and Rumania. The disease was said to resemble the mild typhus reported by Brill and Maxcy in the United States, but small black spots of linear appearance resembling insect bites were often reported "tache noir" and there was no history of lice infestation. It was stated, however, to be different from Brill's disease by the fact that the Weil-Felix reaction was generally negative, but more recently, positive reactions have been frequently reported. Subsequently the infection was observed in Senegal and Sierra Leone (Gordon and Dabey, 1936) and in Pretoria, South Africa, by McNaught and by Pijper (1934). In India, in 1911, McKechnie described a mild, sporadic form of typhus in the northwestern Frontier district, and in 1916 Megaw himself suffered from an attack. Cases have also been described by Scott in Lucknow. In 1932, Combresco reported an outbreak of 34 cases in Rumania. Tickborne typhus has also been reported by Holmes in Australia and by Montierro in Brazil and Patiño-Camargo and others in Colombia.

Transmission.—Fièvre boutonneuse is transmitted by the common dog tick, *Rhipicephalus sanguineus* (Durand, Conseil and Brumpt, 1930). Durand has shown that the dog constitutes the reservoir of the virus. Dogs have been shown to be susceptible to inoculation and their blood has been proved to be infective both for man and monkeys.

A distinctive feature of fièvre boutonneuse is the appearance of the primary sore at the site of the infective tick bite. It varies in size from a pin-head to a pea, and it is not usually painful. Lymphangitis which becomes necrotic or gangrenous subsequently occurs. The initial lesion is known as "tache noir." French investigators have hesitated to include fièvre boutonneuse in the typhus group for the reason that the Weil-Felix reaction, X19, was often negative. The Neil-Mooser reaction in guinea pigs was also reported as negative. Caminopetros (1932), how-

ever, reported in Greece that if an emulsion of infected ticks is injected into guinea pigs these animals react in the same manner as when an emulsion of infected fleas containing the virus of murine typhus is used, a scrotal reaction being observed.

In South Africa the disease closely resembles fièvre boutonneuse and is conveyed by larval ticks, *Amblyomma hebraeum*, *Rhipicephalus appendiculatus*, *Haemaphysalis leachi* and *Boophilus decoloratus*. The small ticks are not found in houses or on domestic animals but are encountered on the grass and attach themselves to man or animals, living in the veld. In this respect the transmission of the disease is somewhat similar to Rocky Mountain spotted fever.

Rickettsiae have been demonstrated in the infected ticks and an emulsion of these has produced the disease in man and animals. In South Africa, however, an agglutination for proteus X strain has been reported, where two forms of this fever have been met with. One is mild, like the kedani fever of Japan, with a local lesion at the point of infection with local lymphangitis. There is practically no mortality. In another form the fever lasts for 8 to 10 days, with a primary sore, severe headache, appearance of rash on the fifth day, stiffness of the neck, and conjunctivitis. A definite Weil-Felix reaction to all three variations of Proteus X has been reported. No animal reservoir is yet known, but Pijper excludes dogs. The immunologic data, Zinsser reports, are confusing. Cases have been reported by Gear and Bevan in Johannesburg, as well as in Kenya. Gear and Douthwaite regard the dog as the reservoir of infection in Cape Colony.

Pijper and Crocker (1938) have found in South Africa a sporadic typhus virus immunologically identical with a virus in rats that protected against tick bite fever but not against epidemic typhus. In Brazil, where the so-called São Paulo typhus is present, the rat is reported by Montierro as the reservoir of the virus and the disease is transmitted by *Amblyomma cayennense*. This is an extremely virulent form of spotted fever. Fialho reports that in this form the Weil-Felix reaction is usually present, but in low dilution. Dias (1938) states that the natural reservoir hosts of the Brazilian form are the opossum, the domestic and wild dog (*Canis brasiliensis*), the wild rabbit (*Silvilagus minensis*), and the agouti (*Dasyprocta*). Vectors are several species of *Amblyomma; A. cayennense*, *A. striatum*, and *A. brasiliense*. Davis (1943) reports experimental transmission of the spotted fevers of Brazil, Colombia and the United States by *O. rudis*, *O. parkeri* and *O. nicollei*. The last is a Mexican species; spotted fever, he says, is not known to occur in Mexico. The spotted fever virus was found to persist through four generations in *O. parkeri*.

Pathology.—Fièvre boutonneuse is distinguished by the occurrence of the local, granulomatous lesion which usually ulcerates. It is accompanied by adenitis of the regional lymph nodes. According to Baltazard (1936), the rickettsiae multiply in this lesion in contrast to their behavior in Rocky Mountain spotted fever. There is no published account of a postmortem examination on a human being. The only histological descriptions are of the maculo-papular eruption by Olmer (1933). Marked swelling of the vascular endothelium is described, accompanied by perivascular infiltration of leucocytes, regional lymphocytes and monocytes. Thromboses are not mentioned. The purpuric

lesions were accompanied by extreme congestion and haemorrhages of the papillary and subpapillary plexuses.

While clinically fièvre boutonneuse, like tsutsugamushi disease, has a local lesion and adenopathy, Hass and Pinkerton (1936) believe that it has generic relationship with the virus of Rocky Mountain spotted fever, and Parker and Davis (1933) and Dyer (1933) have shown that the São Paulo virus cross-immunizes completely with that of Rocky Mountain spotted fever. Plotz (1944) has found that Fièvre Boutonneuse can be differentiated from Rocky Mountain spotted fever by means of complement fixation provided purified rickettsial antigens are used. This test may be employed with convalescent guinea pig or human serum thus providing a convenient laboratory test for diagnosing Fièvre Boutonneuse. There is some cross fixation between this disease and Rocky Mountain spotted fever indicating they are antigenically related.

"Q" fever caused by *Rickettsia burnetti* (*R. diaporica*) has been referred to on page 924. It occurs in Australia and cases have been reported in Montana. It probably exists in other western states since specific antibodies have been demonstrated in the blood of individuals living in Idaho, Montana, Wyoming, Nebraska, Nevada, Arizona and Washington state. Cases reported in Washington, D. C., (Dyer, Topping and Bengston, 1940) were probably due to laboratory infection.

Transmission.—The disease in Australia is believed to be transmitted to man from the bandicoot a marsupial *Isodon torosus* or I. *macrurus* by the tick *Haemaphysalis humerosa.* There is evidence that cattle may also serve as a reservoir of the virus in Brisbane. Derrick (1944) has summarized the Australian outbreak in which 176 cases were diagnosed in Queensland. Nearly all of 129 patients who lived in Brisbane were associated with meat works, most of the 47 other patients worked on dairy farms. Ticks on cattle are probably the source of human infection. It is suggested that inhalation of tick feces is the likely mode of entry of *R. burneti.* Davis (1943) reports experimental transmission of American Q fever by *O. moubata* and *O. hermsi.*

Clinical Features.—The incubation period in the Australian cases has been given as from 10 days to one month. There is an acute onset with fever, prostration, and headache, accompanied by chills and sweats. The acute stage may last from a few days to several weeks. There is no leukocytosis and no rash. In the laboratory cases in Washington, chest pains, coughing, and in some instances rales were present. Some of the cases resembled those of atypical pneumonia of the form described by Longcope (1940).

In a fatal human case reported by Lillie, Perrin and Armstrong (1941) the gross pathological findings were pulmonary oedema and congestion, firm granular consolidation of the upper lobe of the right lung posteriorly and a large soft spleen. Microscopically, the lesions in the lung were those of an atypical pneumonia with much fibrin in the alveoli and bronchioles with a moderate mononuclear cell reaction instead of the purulent one seen in typical bacterial pneumonia. In neither the human lungs, nor in the lungs of infected monkeys, was *Rickettsia* demonstrated histologically.

Diagnosis.—In the second week, complement fixation antibodies against *R. burnetti* have been demonstrated in the blood serum. The organisms had been isolated in guinea pigs by the inoculation of blood

taken during the febrile stage. Protective antibodies have also been demonstrated in recovered cases. The Weil-Felix reaction with Proteus strains has been found to be negative. *Treatment* should be symptomatic. None of the sulfonamide compounds have been found to be of benefit.

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Chapter XXVII

TSUTSUGAMUSHI

(*Japanese River Fever, Mite Typhus, Scrub Typhus*)

Definition and Synonyms

Synonyms.—Flood fever, Japanese river fever, Kedani mite disease Shimamushi.

Definition.—An acute febrile disease caused by a species of *Rickettsia* and transmitted to man by the bite of the larval kedani mite of the region where the infection prevails. The onset is characterized by headache and giddiness, a rather rapidly rising temperature, and swelling of the lymphatic glands draining the region in which is situated a small necrotic ulcer marking the site of the bite. With injected conjunctivae, continuous fever, and hyperaesthesia, the disease continues for about a week, when a macular eruption appears about the face, the chest, extremities and trunk. About 10 days after the appearance of the eruption there is a fall of fever by lysis.

History and Geographical Distribution

History.—There are records which would indicate that the disease has been known for more than 1000 years. The first clinical report of the disease was published by Palm in 1878 and by Baelz and Kawakami in 1879, who gave it the name of river fever, or flood fever, since it was found to prevail along rivers, especially in conjunction with floods. Hatori, 1921, reported that it was identical with the endemic, exanthematic, and bubonic diseases of Formosa.

Geographical Distribution.—It is in the western part of the island of Nippon, when the banks of the Shinanogawa are inundated each spring that the disease has been especially encountered. It formerly was supposed to be confined to Japan, although Ashburn and Craig (1908) thought an affection observed by them in the Philippines was probably identical. Later it was recognized that tsutsugamushi occurs in Formosa and probably in Korea. Fletcher reported cases from a military camp in the Malay Federated States, and it is now believed that Mossman fever of Northern Queensland, studied by Breinl, Priestly and Field (1914), may be a similar affection; cases have recently, 1942, been reported from Cape York peninsula, Australia; Schüffner's "pseudo-typhus" observed in Sumatra is also recognized as analogous clinically and etiologically. More recently the disease has been reported in the Malay States by Dowden and by Fletcher and Field (1927) and by Lewthwaite and Savoor

(1936). The mite-borne typhus has also been reported from Sumatra under the title of "scrub typhus," and by Chopra (1936) in India, where it has been especially studied by Ghosh.

Lewthwaite and Savoor (1940) have found that cross protection tests between the organisms of Sumatran mite fever and the tsutsugamushi of British Malaya performed on rabbits and monkeys confirm the conclusion that they are identical diseases. Kouwenaar also holds this view.

Fletcher has also shown that there are 2 forms of mild tropical typhus in the Federated Malay States, (1) known as the urban type (W form) which occurs in the towns and spreads among the people who are handling grain, while the other form, known as *scrub typhus* (K form) occurs in the country, especially on plantations, and has a close connection with the

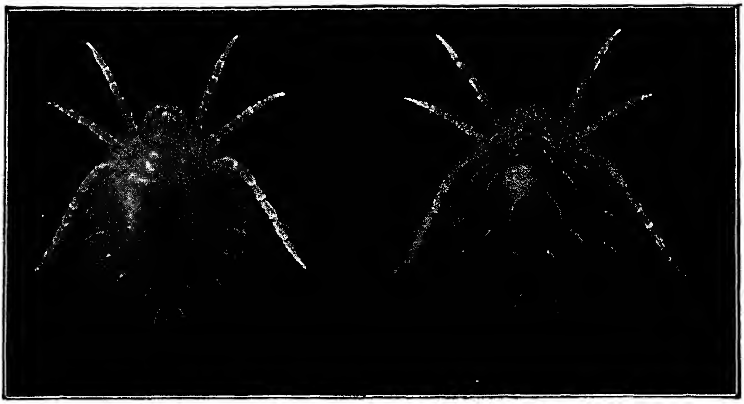

FIG. 220.—The Kedani mite. *Trombicula akamushi.* (From Ruge and zur Verth.)

clearing and pruning of palm trees. It is the K form that is now regarded as caused by a variant of tsutsugamushi virus. Subsequently it was reported that these two diseases in Malaya could be separated serologically (Lewthwaite and Savoor, 1937). The W form is now regarded as a form of endemic murine typhus.

The rural typhus of Malaya, according to Lewthwaite and Savoor, is not accompanied by a primary sore, although in all other features, including serological and infection of animals, it is identical with tsutsugamushi both being transmitted by *Trombicula*. (See page 983.) Kouwenaar (1936) in the Sumatran mite fever found a primary ulcer developed at the point of the bite.

Delbove (1938) has also described a similar disease to tsutsugamushi in Cambodia and in Indo-China.

Etiology and Epidemiology

Etiology.—The work of a number of Japanese investigators has demonstrated the rickettsial nature of the disease. Hayashi (1920) reported as the cause a minute rod, ring-shaped or spheroid body which when stained with Giemsa's stain is demonstrable in the lymphocytes and

endothelial phagocytes of the tissues of the local lesion, of lymph nodes and spleen. The organisms were also observed in the blood plasma and in severe cases in the red blood cells. He was able to transmit the infection to monkeys, guinea pigs and rabbits, and has classified the organism as *Theileria* and named it *Theileria tsutsugamushi*. It has since been shown that it should be classified in the Genus *Rickettsia*. Sellards (1923) proposed the name of *R. niponica* for it. The presence of rickettsiae as the etiological factor has been confirmed by Ogata (1931) (*R. tsutsugamushi*) and by Nagayo et al. (*R. orientalis*).

The virus is present in the blood of a case even in the incubation period, and as little as 0.001 cc. may transfer the infection to the monkey. After the height of the fever has been passed, it may require 0.1 cc. to infect. Spleen emulsions bring about infection, but the virus loses its potency in about 6 hours after death. A temperature of 55°C. for 10 minutes kills the virus. Nagayo found the organism in the eggs as well as in the bodies of mites, but was unable to cultivate it on ordinary bacteriological medium. More recently it was studied in tissue culture (Yoshida, 1935). It also has been shown that the disease may be propagated serially in rabbits by the injection of the virus into the testicle where the rickettsiae are present invading the interstitial cells. Nagayo has also transmitted the virus by intra-ocular inoculation of the guinea pig. The rickettsiae develop within the corneal endothelial cells overlying Descemet's membrane.

Transmission.—The disease is not communicable naturally from person to person and only follows the bite of certain larval mites. In Japan, *Trombicula akamushi* is commonly called the "Kedani mite." It is an orange-red larval mite, scarcely visible to the naked eye, about 400 by 200μ. The mites are very hairy and live inside the ears of the field mice of the area of Japan in which the disease occurs. The adult forms live in the soil of the endemic area. They are about 1 mm. long by 0.5 mm. wide. The hexapod larva usually attaches itself to the axillary or groin regions and drops off after engorgement, leaving an eschar from which adenitis develops. The rickettsial infection, which is transmitted by the larval bite, is inherited from the parent—the larva not feeding a second time. This mite is said only to be a source of danger in regions in which the disease occurs especially along inundated river banks, its bite not producing the disease elsewhere.

Epidemiology.—In Japan and in Formosa the disease is most frequently contracted during the summer, July and August, and less so in June and September, though occasional cases occur in other months. It is particularly during the harvesting of the hemp in the summer that individuals are liable to contract it when bitten by the mite.

The adult mites and nymphs feed only on plants and hence are not parasitic and do not act as vectors. Hayashi has shown that the field mouse (vole), *Microtus montebelloi*, may serve as the reservoir of the virus which is transmitted to man by the larval mite. The mite is found in large numbers on the ears of the field mice, which, however, do not appear to be suffering from any infection.

Monkeys and rats may be experimentally infected by blood or tissues from the human cases and also by the bites of mites or inoculation of their crushed bodies.

Kawamura and Imagawa (1931) have reported the finding of rickettsiae in the salivary glands in collections of *T. akamushi* fed upon infected mice. Kawamura has confirmed the hereditary transmission of the virus.

Rickettsia tsutsugamushi has been studied in tissue cultures (Yoshida, 1935). Wolbach (1940) points out that since it does not invade the nuclei of the mammalian cells in tissue cultures as do the rickettsiae of the Rocky Mountain spotted fever group, it is probable that it does not invade the nuclei of the cells of the vector, an important behavior in classification.

In Malay and Sumatra the disease is reported as transmitted by *T. akamushi*, *T. delhiensis*, and *T. schuffneri*. However, Lewthwaite and Savoor (1936) question whether *T. delhiensis* is a new species. Neither lice nor ticks will transmit these diseases, but the flea can do so under experimental conditions (Nicolle and Sparrow, 1935).

The reservoirs of the Sumatra mite fever appear to be the house rat, *Mus concolor*, and the field rat, *Mus viardii*. In the Malayan tropical typhus, the reservoir is the common house rat, *Mus rattus*. Those who handle hemp, vegetables, grain, wood, hay, in the endemic regions are particularly in danger of infection. Most of the patients are agriculturalists.

Anigstein (1934) states that in Malay the urban disease (W form) is probably the same as Brill's disease, or endemic typhus (flea-borne typhus), while in scrub typhus the actual vector is a mite.

Pathology

No distinctive gross lesions have been reported. Apart from the descriptions of the local ulcer and the swollen regional glands, little that is definite regarding the pathology has been published. The spleen and lymphatic glands have generally been found enlarged and there has been general visceral congestion.

Kitashima and Miyajima (1918) have reported upon the histology of the primary ulcer and the enlarged lymph nodes as consisting of an inflammatory reaction accompanied by necrosis. In the lymph nodes there was fibrinous exudate and necrosis. Similar lesions were noted in infected monkeys. No vascular lesions were described.

Kawamura (1930) also described these lesions in the skin in which there was perivascular infiltration composed mostly of mononuclear vesicular cells and lymphocytes without polymorpholeucocytes. In the former and certain lymph nodes, proliferative and exudative lesions were found, accompanied by necrosis. No changes in the blood vessels and no thrombi were encountered. In the internal organs, miliary necroses were found in the spleen, bone marrow and liver. The presence of lesions in the central nervous system are not mentioned.

Lewthwaite and Savoor (1936) have reported upon the pathology of the rural tropical typhus of Malay. An initial lesion like that observed in tsutsugamushi disease was not found, either in man or infected laboratory animals, either when the animals were infected by mites or by means of

intradermal inoculation. However, on account of cross immunity tests and the ease of transmitting the disease both by intra-ocular and intradermal reactions into rabbits and monkeys, they concluded that the name of "rural typhus" should be discarded in favor of tsutsugamushi. No distinctive pathological lesions were described except petechial haemorrhages in the heart, lungs, alimentary tract and kidneys. However, they observed from histological examination of sections of the brain, small perivascular infiltrations more common in the pons and medulla, but also present in the cerebellum. The cells surrounding the blood vessels were reported as neuroglia cells and lymphocytes. Rickettsiae were demonstrated in the cells of the blood vessel wall. Thrombus formation was noted in some of the capillaries. Focal lesions were also encountered in the brains of infected guinea pigs.

Kouwenaar found in 23 autopsies of mite bite fever in Sumatra similar lesions. There was enlargement of the spleen, congestion of the viscera and of the brain, together with lymphadenopathy. The lesions in the brain were also similar to those found by Lewthwaite and Savoor.

From the information obtainable, it would appear that in tsutsugamushi disease there does not occur the wide-spread thrombotic lesions of the peripheral blood vessels so commonly observed in typhus fever, though thrombus formation has been reported in instances in the capillaries. Wolbach points out that the presence of necroses in different organs suggests that small blood vessels of the internal organs may present lesions leading to thrombosis.

Symptomatology

Incubation Period.—In Oda's series of 14 patients whose contacts could be definitely traced, the incubation period varied from 7 to 12 days, was frequently 8 days, and averaged 9 days from the time of the bite to the onset of general symptoms. In most there was a lack of prodromal symptoms.

It should be noted that many persons bitten by the mite (uninfected) complain of headache, oppression, general malaise, numbness at the site of the bite, anorexia, shivering, and even chills and fever. These symptoms subside in 2 or 3 days and may be caused by the secretions of the mite and not by the disease itself. Such phenomena have been demonstrated experimentally by injecting freshly macerated *akamushi* into volunteers. The infected mite produces not only a local lesion but necrosis.

The symptoms of the disease frequently observed in different localities consist of general malaise, headache, anorexia, insomnia, with dizziness, tinnitus, pains in the joints, and epistaxis. Chills may occur, and more generally constipation. The most important symptom is the tenderness and swelling of lymph nodes, near which one may find yellowish-brown necrotic plaques of skin covered by small crusts. On removing the crusts, ulcers are found which indicate the point of the insect bite. The necrosis in the skin and enlargement and tenderness over the adjacent lymph nodes serve to distinguish the condition clinically from other rickettsial infections, except some cases of fièvre boutonneuse. The spleen is commonly

enlarged and the liver usually is not palpable. Congestion of the nasal mucous membrane, epistaxis and pharyngitis, together with bronchial symptoms, are sometimes present. Hyperaemia of the conjunctivae is almost always present.

A Typical Case.—Usually about 8 days after receiving the bite of the larval mite, which may not have been noted by the patient, there develop chilliness, giddiness and headache, with a rising temperature. In 2 or 3 days from the onset, painful glands are noticed in certain regions, as of the groin, axilla, or neck. From these glands one can often, by following inflamed lymphatics, find the small necrotic ulcer, several mm. in diameter, which is often located in the armpit or in the region of the genitals. There is a dark red areola about the ulcer, which is only slightly tender. The glands are not very much enlarged and are not excessively tender. There may be general glandular enlargement following that of the primary swellings. The pulse rate is usually from 80–100, notwithstanding the rise of the fever to 104°F. or even 105°F.

The body is decidedly hyperaesthetic and the conjunctivae are injected. There is frequently deafness. About the seventh day a macular eruption appears first on the face and then spreads to chest, extremities and trunk. The eruption never becomes petechial. The tongue becomes dry and cracked. There is often a cough. The blood shows a leukopenia. The eruption disappears in from seven to ten days and the fever becomes remittent or intermittent and, after a few days, reaches normal. Parotitis may occur as a complication. A relative immunity follows an attack and in the event of another attack it is less severe.

Pseudo-typhoid Fever.—In the cases described by Schüffner from Sumatra, the necrotic ulcer and glandular enlargements were followed by a roseola which reached its maximum on the eighth to tenth day and was most marked on the trunk and flanks. The nervous symptoms resembled typhoid fever and there was a lymphocytosis. DeLangen (1936) points out that the pseudo-typhoid as described by Schüffner, and later by van Driel, differs from tsutsugamushi fever as seen in Japan in having a much lower death rate and having a lymphocytosis in place of leukopenia and appearing throughout the whole year, although more active from June to August. In a few cases in Sumatra, however, a leukopenia was present.

Schara Boil.—A considerable number of cases of a disease resembling tsutsugamushi were noted by von Rissom in the German troops on the Russian front. He gave the name Schara boil to the disease after the place of its occurrence in Russia. The disease was associated with low-lying swampy tracts and occurred during the late summer and autumn months. There was an abrupt onset with chill, followed by fever and headache, with rather marked swelling of a group of glands, most often of neck, supra-clavicular fossa, axilla or inguinal region. These glands were in relation with a necrotic ulcer. The glands suppurated after 2 or 3 weeks. About a week after the onset an eruption appeared chiefly on backs of hands, extensor surface of forearms, neck and face. Joint pains were occasionally recorded. The fever was an irregularly remitting one and ran its course within 10 days. The ulcers were most common on the face and neck, more seldom on the wrists and ankles. There was no evidence of a part being played by mites. Except for the eruption there is a resemblance to tularaemia.

Symptoms in Detail

The Nervous System.—There is marked giddiness and headache at the onset. Hyperaesthesia of the body is quite characteristic. There is often delirium at night. Deafness is frequently noted.

The Cutaneous System.—A small necrotic ulcer about 1/6 inch (.5 cm) in diameter, with a dusky red areola, is noted at the site of the bite of the larval mite. The healing of the ulcer is delayed well on into convalescence. About one week after the onset a dusky macular eruption appears first on the face (cheeks), then going to the chest, legs, forearms and trunk. It is not marked on neck, arms or thighs. It never becomes petechial. The eruption has been reported on the soft and hard palate and rarely on the buccal mucosa. The eruption may be absent in atypical cases and in second attacks the rash usually does not appear.

Fever Course.—The temperature, which on the first day or two reaches only 101° to 103°F., becomes later on higher and continuous. About the tenth day from the appearance of the eruption it begins to fall, becoming remittent and then intermittent.

The Lymphatic System.—Very characteristic is the swelling of the glands proximal to the initial ulcer. The connecting lymphatics may be inflamed. Later on other glands may show slight swelling and tenderness. The spleen is usually enlarged.

The Blood.—There is no change in the red cells but there is a leucopenia.

Prognosis

The mortality rate reported in Japan varies from 15 to 60 per cent, the higher rate obtaining for older people. After 30 years, the mortality rate increases sharply. Pregnant women usually abort and die. In Sumatra, de Langen gives the mortality as only about 4 per cent, the disease evidently being of a much milder nature. One attack is said to confer some immunity, but reinfection is not uncommon, although usually mild. Second attacks have been reported within a year of the primary one.

Diagnosis

In the differential diagnosis, the limited geographical distribution should prevent error and, in particular, where the initial necrotic ulcer is present, with enlargement of the glands draining the region in which it is located, there should be little confusion. While in plague there is rarely a primary vesicle or ulcer with enlargement of neighboring glands; these glands are matted together and exquisitely tender. Then, too, the eruption of tsutsugamushi and the early and more stuporous state of plague should differentiate, even without the aid of the laboratory.

Tsutsugamushi, typhus fever and spotted fever have many characteristics in common. These diseases may be differentiated somewhat by the course of fever and eruption as shown in the following table, which illustrates the symptoms which are more commonly observed.

	Fever course	Eruption
Tsutsugamushi..........	Fever increases each day until reaching maximum about 4th or 5th day. Fall by lysis after fading of eruption.	Begins on face, then chest, legs, forearms and trunk. Does not become petechial. First appears about 7th day.
Tabardillo. Typhus fever. Brill's disease.	Onset and termination of fever characterized by considerable abruptness. Very striking mental symptoms.	Begins in axillae and flanks, thence going to abdomen and extremities. Avoids the face. Petechial tendency. First appears about 5th day.
Spotted fever of the Rocky Mountains.	Gradual or fairly rapid rise during a week with lysis commencing at end of second week continuing through third week.	Begins on forearms and leg. Petechial tendency. May have gangrene of prepuce and scrotum. First appears on 2d to 5th day.

The Weil-Felix reaction is frequently of value in diagnosis. In tsutsugamushi disease there is usually a positive agglutination in moderately high titer with the strain OXK, while the serum gives a negative reaction with OX2 and OX19, this differentiating the disease from typhus and spotted fever. Unfortunately in some of the milder forms of the disease occurring outside of Japan these reactions are less constant and hence of less value. However, the negative agglutination with OX2 and OX19 is usually the condition and hence of value in excluding true typhus infection. In some atypical cases in which only a low agglutination titer for OXK is found and where there is an absence of doubtful primary lesion and rash and absence of leukopenia, animal inoculation and cross immunity tests may be necessary to establish the diagnosis. Fever, and often scrotal reactions, are observed by the inoculation of guinea pigs. The inoculation of rats usually gives inapparent results.

Prophylaxis and Treatment

Prophylaxis.—In mite-infected countries, the body should be protected by proper clothing. For this purpose, in Japan, a mite-proof suit has been devised and should be worn especially by those harvesting hemp during July and August. It has also been suggested that laborers should dust their bodies with a powder consisting of equal parts of flowers of sulphur and talcum as a repellant for the mites. Dimethylthallate has been particularly recommended. The larval form of *akamushi* may be effectively destroyed by spraying the infested ground with petroleum emulsion. Excision or cauterization of the area of the bite has been suggested, but it is not clear that this has been of great value.

Prophylactic inoculation has not yet been demonstrated to be of value. Kawamura (1937 and 1939) found that inoculation of a weakly virulent

strain of tsutsugamushi fever produced a mild illness in a man, followed by immunity to inoculation with a strongly virulent strain. However, obviously this method could not be recommended for general employment. Lewthwaite (1939) has been unable to confer any immunity against tsutsugamushi infection in guinea pigs by means of different prophylactics prepared from suspensions of *R. orientalis* sterilized with formol, phenol, or by other vaccines.

Treatment.—Salvarsan has been found valueless and drugs are indicated only symptomatically, especially to combat the insomnia. Hayashi and Mukoyama have recommended the use of immune serum for the treatment of severe cases. Serum therapy is still in the experimental stage.

Scrub Typhus

Scrub typhus has extreme military importance because of its prevalence in the Southwest Pacific area and the China-Burma-India theater.

Sapero (1944) reports that scrub typhus has occurred in our armed forces in New Guinea, usually in outbreaks which have been in sharply localized areas. The infected areas appear to be Kunai grass meadows and adjacent jungle margins. Several species and several genera of mites are prevalent in the areas concerned with the outbreaks, but to date, no one species has been definitely incriminated as a vector. It is suspected that certain species of jungle rodents may serve as an animal reservoir for the disease, but on this point evidence also is still largely lacking.

Lipman, Byron and Casey have studied 101 cases occurring in New Guinea in which there were 8 deaths, giving a case mortality rate of 7.9 per cent. In two of the fatal cases there was a clinical diagnosis of large pulmonary emboli occurring after the acute febrile period of the disease had passed. The average duration of the febrile period was 17 days. It varied between 10–27 days.

Physical examination often revealed an eschar representing the site of the bite. In this series 70 per cent showed this lesion with marked regional adenopathy. By the fifth to the eighth day, 85 per cent of the cases showed a maculopapular erythematous rash on the thorax or abdomen. The rash lasted eight to twelve days. Bronchitis developed in about 30 per cent of the cases. The cardiovascular system was also profoundly affected. The Weil-Felix reaction with *Proteus OXK* was positive in every case by the second week. In critically ill patients a titer of 1:160 was held to be diagnostic. In the milder cases, the titer ranged from 1:640 to 1:2580 by the 16th day. The treatment was symptomatic.

Corbett (1943) has studied the pathology in 7 cases of scrub typhus and given a brief clinical abstract of each case. An acute diffuse myocarditis, characterized by a perivascular and interstitial infiltration with mononuclear cells and occasional neutrophiles and eosinophiles, was found in every case. Damage to the myocardial fibers varied in degree. The vascular endothelium was usually swollen. In places the arteriolar walls were thickened and degenerated and showed intramural round cell infiltration. In one case a mural thrombus was seen in a small subendocardial vessel. In the lungs a lobular pneumonia was present in three cases and a hemorrhagic infarct was noted in one instance. In the liver in several instances there were areas of focal necrosis. The spleen showed engorge-

ment and in one instance a thrombosed vessel was seen in the region of an infarct. In the gastro-intestinal tract, enlargement of the lymphoid follicles was seen in several cases. The kidneys showed congestion in all cases and small foci of perivascular round cell infiltration and interstitial hemorrhages were frequently noted. The brain was examined in 4 cases. A constant characteristic was a lesion consisting of perivascular proliferation of glial cells and infiltration with lymhpocytes. The vessels showed swollen degenerated endothelium and in several there was intramural round cell infiltration with necrosis of the intimal and medial layers. The conditions found correspond well to those described by Lewthwaite and Savoor and Kouwenaar described on page 979.

Ahlm & Lipshutz (1944) have also reported upon 76 cases of Tsutsugamushi fever in the southwest and have summarized some of the observations of others.

Bullis Fever

During the spring and summer of 1942, among soldiers engaged in field exercises at Camp Bullis, near Houston, Texas, a febrile infection was observed in which all the patients had multiple tick bites by *Amblyomma americanum* shortly before the onset. According to Woodland, McDowell and Richards (1943) who observed 33 cases, the fever lasted from 3 to 13 days. The onset was abrupt; most of the patients had post-orbital headache or occipital headache, the fall was by lysis, and there was no further rise except in a few instances in which an occasional rise to 99°F. was observed. All the patients had enlargement of at least one set of lymphatic glands, while general adenopathy was common. The throat was slightly red and injected. In the more severe attacks (10 per cent) a maculo-papular rash was seen on the trunk early in the course of the fever; it never lasted more than 48 hours, and resembled the rash of endemic typhus. There was pronounced leucopenia on the 2nd or 3rd day. The blood of six patients was tested at the National Institute of Health Laboratory; completely negative findings were reported for fevers of the typhus group, undulant fever, tularaemia, typhoid and paratyphoid A and B. Inoculation of guinea pigs, rabbits and chick embryos, revealed no causal agent.

Livesay and Pollard (1943) report that guinea pigs inoculated by the intracerebral route with spinal fluid from patients developed a transient mild fever on the 9th day in several cases. In one case a serial passage was successful but there was no apparent increase in virulence. Brain substance from reacting guinea pigs inoculated by the intravenous route into developing chick embryos caused their death within 6 to 9 days, and the same result was obtained in 5 serial transfers by the same route.

Guinea pigs inoculated with the blood of patients by the intraperitoneal route showed a low-grade febrile reaction lasting 2 days which occurred consistently on the 9th to the 10th day. There was no scrotal reaction, but in 2 cases an aseptic fibrinous peritonitis was observed. Smears from the spleens and peritoneal scrapings from the guinea pigs showed small red-stained rods and coccoid bodies in the cytoplasm and nuclei, when stained by Machiavello technique. Similar results were obtained in specimens from the enlarged lymph nodes of two patients and emulsions of such lymph nodes also caused a febrile reaction in guinea

pigs. About 150 ticks, mostly *A. americanum* were collected at random in the affected area and tested by guinea pig inoculation. One positive result was obtained in which intracerebral inoculation caused a rise of temperature to 106.2°F. for 24 hours on the 9th day. By intravenous, serological, and other tests, Rocky Mountain spotted fever, typhus fever, Q fever, Chaga's disease, equinine encephalomyleitis and lymphocytic coriomeningitis, were also excluded. It was concluded that Bullis fever was a previously undescribed syndrome, apparently caused by *Rickettsiae*, which may be transmitted by an arthropod vector in the Camp Bullis Area.

Parker and Steinhaus report that at the U. S. Public Health Service Rocky Mountain Laboratory about 10,000 *A. americanum* and about 2,500 mites from Camp Bullis were tested for infectious agents. The mite tests were negative. However, a number of strains, all of the same rickettsiae have been recovered from the ticks. Guinea pigs and white mice are susceptible to it. This rickettsiae cross immunizes with *Rickettsiae diaporica*, the agent of American Q fever. It is either identical with it or closely related but the infection caused in guinea pigs differs somewhat, being irregular and less marked. Further study of the infection would seem desirable.

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TRENCH FEVER

Synonyms and Definition

Synonyms.—Pyrexia of unknown origin (P.U.O.), Meuse fever, Volhynian fever, shin fever, quintan or five-day fever.

Definition.—Trench fever is a specific, infectious, febrile disease in which the virus is present in the blood and sometimes in the urine, and is commonly transmitted from man to man by the body louse, *Pediculus humanus* (*corporis*). It is characterized usually by an enlargement of the spleen and an eruption consisting of small, erythematous spots or papules; headache, dizziness, pain in the legs, especially the shins, the back, and behind the eyeballs, injection of the conjunctivae, and a sharp rise in temperature to 103° or 104°F. In the majority of the cases, the fever or other symptoms assume a relapsing character. No single symptom or characteristic of the disease yet recognized is pathognomonic. Death practically never occurs.

History and Geographical Distribution

History.—Trench fever is one of the infectious diseases regarding which our knowledge has been obtained as a result of the World War. It is remarkable that so striking and communicable an affection as trench fever should have been an unrecognized entity prior to that period. For this reason, it was suggested that it had been introduced by colonial troops into the armies in northern Europe, where it attracted particular attention by its prevalence; or again, that, as the armies in the field were more or less exposed to medieval conditions, hence a return to medieval diseases hitherto imperfectly known, might be expected. One can only conjecture as to whether the quintan fever described by Hippocrates, Galen and Razes, was the disease known today as trench fever. Clinically it might in earlier years frequently have been mistaken for malaria or European relapsing fever. As there is no specific diagnostic laboratory method known for trench fever, even today, it is probably often confused with other diseases.

As to the suggestion that the disease may have been introduced into Europe by colonial troops, it may be said that trench fever does not definitely correspond at least to any of the well-recognized exotic forms of fever. While resembling dengue in some respects, and relapsing fever in others, as well as various well-recognized exotic fevers, there is no satisfactory account of the prior existence of such a type of fever. Some

have thought that the miliary fever reported in France from 1821 to 1855 might have been a type of trench fever, since it had no mortality.

The Epidemic of 1915–1918.—During the latter part of 1915 and in 1916, the occurrence of a disease characterized by febrile relapses became gradually recognized in some of the armies in northern Europe. It was first referred to in Flanders and France by Graham, and Hunt and Rankin; McNee, Brunt and Renshaw first described it under the name of trench fever. Herringham also called particular attention to it and stimulated its further study. Werner described cases of a similar affection in German or Austrian troops in Volhynia and Poland.

McNee, Brunt and Renshaw did much to establish the specificity of the disease, and were able to demonstrate that the infectious agent was present in the blood and that the disease could be transmitted from man to man by direct inoculation of the blood.

There was much speculation as to the nature of the infectious agent and the method of its spread. It was suggested by some to be spread by rats or mice. Just as in the case of malaria and yellow fever before the proof of their method of transmission was demonstrated, so in trench fever a number of observers had suggested the disease was conveyed by insects. Flies, mosquitoes, fleas and lice were all suggested as being concerned in its transmission.

In October and November 1917, the writer being cognizant of the enormous loss of man power which trench fever was causing in some of the allied armies and of the great danger of its introduction and increase in other armies, made a formal offer to attempt to determine definitely and with properly controlled experiments the method of transmission of the disease, which obviously was the most important problem in connection with its prevention. This offer was accepted, and after the necessary authority had been obtained from the American and British military authorities in January 1918, and the writer had secured the detail of six other medical officers, two non-commissioned officers from the American Expeditionary Forces, and one medical officer from the British Expeditionary Forces* to assist in carrying out these investigations, as well as a detail of eighty-six enlisted men from the United States army who had volunteered to submit to the necessary experiments, the work was undertaken.

At the same time the British War Office also appointed a commission to study trench fever in London, with Surgeon-General David Bruce as chairman, and Major W. Byam as supervisor of the clinical and experimental work.†

In the work of each of these two commissions there was close and friendly cooperation. The British Commission carried out its work in London upon civilian volunteers and in well equipped laboratories, while the American Commission carried out its investigations in improvised laboratories in the field. The latter commission, however, had the advantage of securing young and healthy volunteers from the United States army for the experiments and a plentiful source of supply of acute cases of trench fever.

Both of these Commissions demonstrated from well controlled experiments on human volunteers that the infectious agent is present in the

* *The names of the members of the Commission that carried out these investigations were H. F. Swift, E. L. Opie, W. J. Macneal, W. Baetjer, A. M. Pappenheimer, A. D. Peacock and D. Rapport, in addition to the writer.*

† *The other members of this Commission were A. Bacot, D. Harvey, H. Plimmer, H. French, J. A. Arkwright, P. M. Fletcher and A. F. Hird.*

blood during the disease and that the disease is transmitted by the louse, *Pediculus humanus*.

Practically all of the important knowledge we possess regarding trench fever is to be found in the two reports of these commissions.

Geographical Distribution and Prevalence during the World War

The disease was observed during the war particularly in troops in Flanders, France, Poland, Galicia, Bukovina, Italy, Salonica, Macedonia, Mesopotamia and Egypt. Certain areas within these countries were particularly infected. It was one of the largest sources of wastage of man power in the combatant forces. From 1915–1918 it has been estimated that it was the cause of from one-fifth to one-third of all cases of illness in the British armies in France, and of about one-fifth of all diseases in the German and Austrian armies. It was introduced into the American troops in the American sector after its method of transmission had been discovered, where its wide spread was prevented. The disease evidently found conditions most favorable to its spread among troops in the field heavily infested with lice. It is interesting to note that at the present time (1940) neither cases of trench fever nor of Weil's disease are being encountered in certain regions in Flanders where they were during the war so common among troops. However, several German reports of the occurrence of outbreaks of the disease, have been made in 1943.

Etiology.—The blood in the active stages has been shown to contain the infectious agent. This was first demonstrated to be the case by McNee, Brunt and Renshaw, and later the American Commission confirmed this fact and further demonstrated the fact that the virus is present in the plasma of the blood. It was also shown that the virus is sometimes excreted in the urine in trench fever, and that it was possible to infect human beings by the inoculation of a small portion of the urinary sediment from trench fever cases.

Method of Transmission.—The disease is transmitted commonly by the body louse, *Pediculus humanus corporis*, living under practically natural conditions as was first demonstrated in an entirely conclusive manner and by properly controlled experiments by the American Research Commission. In these investigations 103 different human experiments were carried out upon volunteers from the American army in connection with the study of the transmission of the affection. In the first group of experiments in connection with its transmission by lice, twenty-six men were exposed to lice that had bitten trench fever cases in the febrile stages of the disease, while four other men were exposed for the same or a longer period of time to normal, uninfected lice which had only fed upon healthy individuals. After a period of over three months, in order to show whether the men who had been exposed to the normal lice were or were not naturally immune to trench fever, three of them were subsequently exposed by other methods to trench fever infection. All of them contracted the disease. Of the twenty-six men in the first group who were exposed to lice that had fed upon cases of trench fever, twenty, or seventy-six per cent, developed this disease. On the other hand, the two exposed to many

hundred lice newly hatched from eggs laid by lice, which had fed on trench fever cases, did not contract the disease. Thus no evidence was obtained of hereditary transmission of the virus of trench fever in the louse. In the three instances in which lice taken from the clothing of trench fever cases were employed for infection, two of the individuals exposed to such lice contracted the disease

After having shown conclusively by fourteen positive experiments in the first group that the louse transmits the disease living under natural conditions, experiments were performed to show whether this insect may transmit the disease by its bite alone when living under natural conditions or under unnatural ones in entomological boxes and biting through chiffon, and when no scarification or scratching of the skin and no crushing of the lice occurred. Five experiments of this nature were performed, all of which resulted positively.

From other experiments it was shown that practically all virus-free, control lice become infective about 9 days after feeding on febrile patients.

In eight experiments with volunteers it was shown that trench fever may be produced in an artificial manner by scarifying the arm and rubbing in, as in vaccinating against smallpox, a small amount of the excrement of lice which had fed upon trench fever cases. The British Trench Fever Commission first demonstrated this method of infection, the excreta being collected from the sixth to the nineteenth day after first feeding upon the patient. In these instances it was found that the incubation period of the disease varied from seven to eleven days.

The Virus.—During the World War very extensive investigations regarding the specific microorganism of trench fever were made and a large variety of organisms, both bacterial and protozoal in type, were described as the probable causative agent by various investigators working with the hope of discovering the cause and eliminating this disease. From these different investigations it was evident that the etiology of trench fever had not been entirely definitely determined.

As trench fever like typhus fever is transmitted by *Pediculus humanus corporis* and as extracellular *Rickettsia* have been found in some lice fed on trench fever cases, it has seemed to a number of writers a natural assumption that trench fever is also caused by *Rickettsia*. Some observations suggest this and it may be true, and for obvious reasons it is a temptation to accept it as a fact. Nevertheless, it must be admitted that this fact has not yet been demonstrated by scientific experiment and the evidence should be reviewed. *Rickettsia* have never been demonstrated in man in this disease, nor have the vascular lesions in the skin, so characteristic of rickettsial infection, been noted. The trench fever infection has not been transmitted to any animal, as is the case with rickettsial diseases. Mice, rats and guinea pigs inoculated with the infected blood of trench fever, first by McNee, Brumpt and Renshaw and later by the American Commission, have been negative. It is true that Topfer found extracellular *Rickettsia* in lice fed on Trench fever cases and in lice fed on cases of Trench nephritis (which was not regarded as an infection), and that

Arkwright, Bacot and Duncan (1919–1920) found that some of the lice fed on trench fever cases showed extracellular *Rickettsia*.

However, one cannot disregard the experimental work of Munk and Rocha Lima, of Sikora and Brumpt, Hindle and the writer, which conclusively demonstrated that *Rickettsia* were found in normal lice fed on healthy people, in a locality free from trench fever, and that such *Rickettsia* were apparently identical with those found in some lice fed on trench fever cases, as well as with those found in lice fed on patients with other diseases, and moreover, that such lice fed on other healthy people produced no disease.

Sikora, in emphasizing that *Rickettsia* have not been shown to be the cause of Volhynian fever, found that of 100 healthy, lousy persons, not less than 13 harbored lice showing *Rickettsia*. With the contents of such rickettsia-containing lice, guinea pigs were inoculated into the heart, and young mice subcutaneously, but the animals did not show any pathologic reaction. Sikora then injected herself intravenously with the contents of two such infected lice, and later subcutaneously with the contents of the alimentary tract of ten such lice, without any infection. Brumpt also collected lice from healthy prisoners and found them heavily infected with *Rickettsia*. He fed seventy of these upon himself and remained healthy. Bacot, who fed lice on himself at intervals for a long period, developed a fever when in Poland, and it was suggested that he had Trench fever.

Wolbach suggested that there may be evidence in this that *Rickettsia* cause trench fever, because of 27 lice that were fed upon Bacot when he had this fever in Poland, 17 developed extracellular (never intracellular) *Rickettsia*. But it must be kept in mind that it has been conclusively demonstrated by at least six investigators mentioned above that lice fed on healthy people, or those suffering from other fevers, may show these extracellular *Rickettsia*, and that diagnosis of a single case of trench fever is often very difficult and that there is no proof that trench fever was prevalent in Poland at that time. However, as typhus was prevalent at the time in Poland and no trench fever was reported as being present in the region, it has been suggested that some of the lice which had fed upon Bacot were infected with a few *Rickettsia prowazeki* of typhus as well as with the extracellular *Rickettsia* which occur not uncommonly in normal lice. It would be quite impossible to exclude the presence of a very mild infection of the louse with *R. prowazeki* by a microscopical examination of the louse alone. Bacot is supposed to have later died of typhus. In any case, to attempt to establish the etiology of a disease upon a single doubtful case is dangerous, and if the organism found in the lice fed upon Bacot were believed to be other than *R. prowazeki* it is unfortunate no study was made of them. Wolbach admits that the question of deciding the specificity of *Rickettsia* for trench fever is a most difficult one, also whether *Rickettsia pediculi* is the cause of Trench fever. Zinsser (1940) states that he omits trench fever in his discussion of the rickettsial diseases of man as it stands somewhat apart in clinical characteristics and because he thinks we possess too little experimental knowledge of the responsible virus to define its precise relationship. Pinkerton (1936) points out that it is theoretically possible to establish strong presumptive evidence of trench fever by feeding carefully controlled lice on patients to see if they acquire rickettsiae. However rickettsiae sometimes develop in lice fed on normal individuals. On the other hand lice containing *R. pediculi* or *R. quintana* fed on healthy individuals have not produced Trench fever. It has been suggested that *R. pediculi* is similar in the louse to *R. melophagi* in the intestine of the sheep ked, both being non-pathogenic for man.

Trench fever is a relapsing fever and is not a fatal disease. In this latter respect and in some other features it resembles dengue fever, though unfavorable sequelae sometimes develop in trench fever. The experimental evidence has shown that dengue fever is due to a filtrable virus (Ashburn, Craig, 1907) (Siler, Soule, 1925–1928) and others. While the virus of trench fever is not filtrable, as it occurs in the blood, several experiments have indicated that this virus in a suitable medium, as urine, may occasionally pass through coarser filters, even though such passage is unusual (American Trench Fever Commission, 1918; Bradford, Bashford and Wilson, 1919).

In a study of dengue, Siler and Sellards (1928) found in about half of the mosquitoes (*Aëdes aegypti*) fed upon patients masses of *Rickettsia* in the lumen of the hind gut and in smaller numbers lying within the epithelial cells.

If it should later be proved that trench fever is caused by extracellular organisms in the intestines of lice, as *Rickettsia pediculi*, it will be necessary to modify the definition of the genus *Rickettsia*, which originally referred to intracellular microorganisms. All of the known pathogenic species of *Rickettsia* occur intracellularly.

Mosing (1936) described an interesting epidemic among people employed in feeding laboratory reared lice used for the purpose of preparing Weigl's vaccine against classical typhus. He stated that the organisms found in the lice that had bitten the individuals differed from those of epidemic typhus by reason of their greater size, extracellular position, and non-pathogenicity in the louse. He suggested the name of *R. weigli* for this organism.

Somewhat similar infections were reported in Russia by Yakimoff (1926); in Japan by Ogata (1935) and France and Spain by Schapiro (1939). The relationship of these outbreaks to endemic typhus has not been clarified.

Pathology

The disease constitutes a mild specific form of septicaemia and the symptoms of it are obviously due to the action of the toxins of the virus which circulates in the blood and is excreted at least partially in the urine. The virus may sometimes persist in the circulating blood for as long a time as 300 days from the beginning of the disease, as was demonstrated by the British Commission. In chronic cases the toxins of the virus give rise to a more or less cachectic condition. As there are no records of autopsies in trench fever cases, the disease being practically never fatal, no histological investigations have been carried out except in connection with the maculae of the skin. Schminke has reported that the corium of the trench fever macule is hyperemic and oedematous, and that there is a perivascular lymphocytic infiltration with a variable number of polymorphonuclear leucocytes. The skin lesions differ from those seen in typhus fever in that there is no necrosis of the endothelial cells of the vessel wall and no hyaline thrombosis. It has been suggested that the segmental area of cutaneous hyperesthesia may arise from inflammatory changes in the dorsal nerve roots.

Symptomatology

Incubation.—The incubation period of the disease in nature probably varies between ten to thirty days, though, if the infection is acquired from a very large amount of the virus, this period may be somewhat shorter. In the cases in which the disease was produced by artificial methods of infection, such as the intravenous injection of blood or one of its constituent elements, or by scarifying the skin and rubbing in the virus either in the louse excrement or in the urinary sediment, the incubation has usually varied from five to twenty days, and with lice living under practically normal conditions from fourteen to thirty days. During the incubation period the patients sometimes show prodromal symptoms, shortly before the onset of the attack of fever, consisting of malaise, headache and pains in other parts of the body.

Clinical Features.—The most characteristic clinical features of trench fever are the sudden onset, accompanied by headache, dizziness, pain in the legs, especially the shins, the back and behind the eyeballs, particularly when moved, nystagmus on turning the eyes completely sideways, injection of the conjunctivae and a sharp rise of temperature to 103° or 104°F. The fever in over one-half of the cases subsequently assumes a relapsing character. Enlargement of the spleen and the appearance of small erythematous spots or papules occur in from seventy to eighty per cent of the cases. The erythematous spots are observed particularly over the chest, back and abdomen. They are usually not raised above the surface of the skin, are pink in color, disappear on pressure and generally measure about two to four mm., although sometimes they may measure from four to six mm. in diameter. Occasionally the rash is distinctly papular in character. In number the spots vary from several to one or two hundred. They often disappear in less than twenty-four hours after their appearance, and they may occur as early in the fever as on the second or third day, or be first observed just prior to or during a relapse. While no one of these symptoms given above can be regarded as characteristic or constant, the presence of several or all of them usually serves to make an accurate diagnosis of trench fever during outbreaks.

The urine often shows a trace of albumin, but evidence of true nephritis is not present in the uncomplicated disease. In a small percentage of the cases frequent desire of micturition is complained of, and Byam has shown that polyuria is common. The leucocyte count is very variable. There is frequently a leucocytosis and the leucocytes may rise at the time of the relapse. In other cases, however, the count may be normal or there may be a leukopenia. It has been suggested that in patients with persistent pain in the shins a steady high count probably indicates a continuation of the infection.

The fever does not always follow a definite type, but may consist of, first, a short attack, lasting for about a week, with sometimes but not always, after a few days, a single short rise; second, a more prolonged initial fever, sometimes lasting for six or seven weeks, with relapses not distinctly

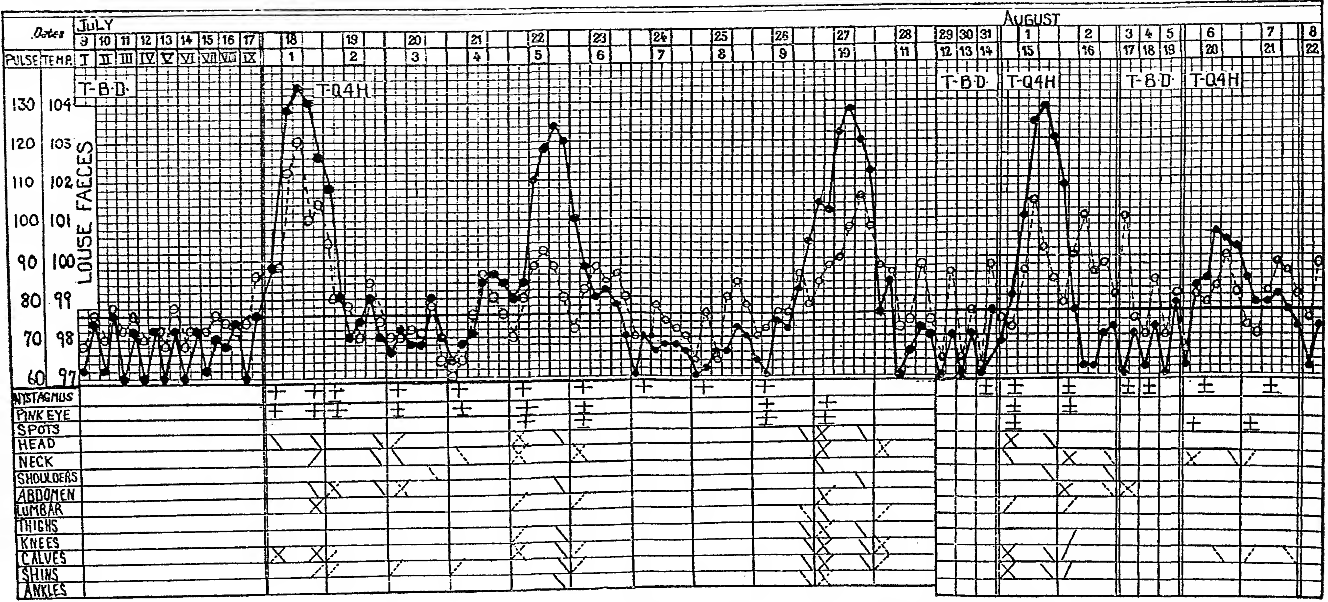

FIG. 221.—Temperature chart of experimental trench fever infection. (From report of American Red Cross Research Commission.)

marked; and, third, a more regularly relapsing fever, with more or less definite normal intervals, lasting from five to seven days. Many variations in these types of fever are seen, and in some of the patients there may be a long fever lasting from forty to sixty or more days with only very slight remissions.

It has been shown by the experimental transmission of a strain of trench fever virus through several generations in man, either by means of the direct inoculation of the infected blood or through the agency of infected lice, that all these main types of fever are common in this disease, and, moreover, that the type of fever which appears in an inoculated case does not necessarily conform to the type observed in the original patient from which infected blood was taken.

The number of relapses varies greatly; from three to five periods are common, and some have as many as six or seven relapses. Several of our patients, who had been entirely free from fever for from six to seven weeks or longer, developed typical relapses. In these cases reinfection could be definitely excluded. In some of the cases at the time of the relapse the temperature may remain normal, but a marked increase of the pulse occurs and other symptoms of the disease appear. Occasionally relapses persist as late as a year or more after the original attack.

Tachycardia and the condition known as D.A.H. (disordered action of the heart) of soldiers have been described as frequent complications or sequelae particularly in cases of the disease occurring in soldiers attacked while performing heavy military duty, or in those returning to such duty before completely well. Carmalt Jones has found that among 100 cases of disordered action of the heart taken at random, and serious enough to reach a heart center, two out of three were due to trench fever alone, and eight out of nine were due to this infection at least in part. In a group of patients Swift noted the position of the apex impulse from day to day, and on several occasions observed the shifting of the apex impulse from well within the nipple line to an inch or more beyond it. Also the area of cardiac dullness had apparently increased in width. Concomitant with this change there had been a distinct increase in pulse rate. Whether these signs indicate an actual change in the size of the heart or not is questionable, but at least they indicate a distinct alteration in the condition of the heart. Swift has made a careful study of the symptoms.

Occasionally a picture somewhat resembling paroxysmal tachycardia is seen during the course of trench fever. Precordial pain and hyperesthesia are not infrequently observed. Accompanying these symptoms and signs directly referable to the heart, there is at times dyspnoea, even with the patient in bed. It is also not an infrequent symptom when the patient is up and about. However, as these symptoms and signs are also found with certain other infections, they cannot be regarded as peculiar to trench fever.

Areas of tenderness are frequently associated with the pains in the head, legs and back, already referred to and may involve skin, muscles, tendons, bones or joint cartilages, although the nerve trunks themselves

do not appear to be involved. The area of skin found by the British Commission to be most hyperalgesic was that running from knee to ankle along the outer border of the tibia. Byam and Carmalt Jones found that the areas of skin tenderness seem to correspond to the eighth cervical, first and seventh dorsal and the first to fifth lumbar segments of the cord. The whole of these segmental areas were involved in comparatively few cases, those most commonly involved being the lower segments of the lumbar group. Sundell showed that areas of analgesia might be detected in some of the more prolonged infections, the loss of sensibility varying in degree from a mere blunting of sensation to complete analgesia. The most common situations for this phenomenon were the outer surface of the calf, the infrapatella, the scapula and deltoid regions. With reference to these pains and areas of tenderness it is interesting to refer to the cases in the later stages of the disease described by Rudolph and Soltau, under the term of trench fever cachexia. Soltau found that not less than seventy per cent of cases diagnosed in the British army as myalgia were really suffering from trench fever. Lloyd also describes subacute cases of trench fever diagnosed as rheumatism, myalgia or neuritis.

Chronic Cases.—The British Commission found that in a large proportion of the cases of trench fever invalided to England, there is a tendency to advance through a subacute towards a chronic condition with symptoms of disorganized action of the heart and in some cases symptoms of neurasthenia. The symptoms met with in these cases were summarized in the order of their importance as follows: exhaustion, giddiness and fainting, headache, breathlessness on exertion, pain, irritability, lassitude, sweating, coldness of the extremities, palpitation and cardiac irregularity, fever. The majority of the chronic cases presented all of the above symptoms. Byam believes that considerable evidence exists which points to a specific action on the vagus in such cases.

Differential Diagnosis

During epidemics, typical cases are usually readily diagnosed from the symptomatology outlined above.

While there is no specific laboratory method of diagnosis for trench fever, laboratory examinations are often of assistance in differentiating this disease from other infections, such as malaria, European relapsing fever, tick fever, seven-day fever and Weil's disease without jaundice. Here it may be merely stated that neither spirochaetae nor the *Leptospira icterohemorrhagica* has ever been encountered in undoubted trench fever cases; that the general character of the disease and particularly the relapsing character of the fever and the nature of the rash are quite different from what has been observed in typhus. From typhoid and paratyphoid fever it may be distinguished by the absence from the blood, stools and urine of trench fever cases of organisms of the enteric group. Marris believes that the "atropin test" is of value in differentiating trench fever from the enteric group since the toxins of trench fever stimulate while those of enteric depress the nervous system (see Typhoid fever p. 1616).

The absence of marked catarrhal symptoms usually (though not always) serves particularly to differentiate the disease from influenza, while the character of the rash and the differential leucocyte count serve to distinguish trench fever in the early stages of the disease from dengue fever. In epidemic jaundice not only the presence of the *Leptospira icterohemorrhagica*, but the nephritis, and usually the jaundice, serve to distinguish this disease from trench fever. Pain in the muscles of the neck in trench fever may at times be so severe as to resemble the neck pains of meningitis, and the abdominal pain may simulate that of appendicitis, so that cases of this disease have been operated upon for appendicitis by mistake. However, the abdominal pain of trench fever is elicited by superficial palpation rather than by deep, firm pressure, and, as a rule, there is no confusion between these two conditions. Undulant fever obviously may be differentiated from trench fever by the detection of the *Micrococcus melitensis* in the blood or by the agglutinating reaction of the serum with this organism.

Prognosis

The importance of the disease has particularly depended upon its wide prevalence, heart complications and great loss of service caused by it during the war. Generally the prognosis in properly treated cases is good and the disease is practically never fatal. It has been estimated that of men in good health at the time when afflicted with the acute disease, about 85 per cent were ready for return to duty in two months from the time of onset. However, this statement does not apply to the subacute or chronic cases, and the occurrence of subsequent relapses in some of the 85 per cent of recovered acute cases cannot be excluded. Of 236 advanced cases of the disease treated at Hampstead, England, giving an average disability of 4.5 months, only 6.2 per cent left the hospital free from symptoms, while 7.2 per cent were returned to civil life as permanently unfit. Of those discharged from the hospital after 9 months, 60 per cent had still shown greater or less evidence of the persistence of the disease during the time since their discharge. In relation to prognosis, the immediate placing of the patient at rest in bed at the time of onset and during all active symptoms of the disease is important. In the subacute and chronic stages a steady gain in weight is said to constitute the most reliable guide to a favorable prognosis. Men below 35 years of age are more likely to entirely recover in a shorter period of time than men above that age.

Treatment

The treatment should be symptomatic. For the pain, aspirin is usually satisfactory but in some cases codeine may be necessary to control severe pain.

Up to the present time no specific remedy for the disease has been found. Sweet and Wilmer, and Richter have reported favorable results from the intravenous injection of 10 cc. of a 1 per cent solution of collargol, but these observations have not been further confirmed. The British

Commission also employed intravenously a large number of drugs such as acriflavine, galyl, collosol argentum, iodine, antimony, sulphur, manganese palladium, colloidal rhodium, intramine, kharsivan, eusol, trypan red, tartar emetic and disodoluargol, but without favorable results.

Swift has emphasized that as long as two or three of the positive signs of the disease persist one should regard the infection as still active. The patient should not be allowed to get up and be about until it is evident that the infection has been entirely overcome. As a rule it is advisable not to allow the patients up until they are well past the time of an anticipated relapse. The time which the patient is allowed to be up should be progressive, beginning with a few hours at a time. If during this increase of exercise there is unusual tachycardia or return of any of the symptoms, the time of sitting up should not be increased, and, if these symptoms persist, the patient should be returned to bed. After the patient has been allowed to be up all day without unfavorable symptoms, he should be placed on a course of graded physical exercise. The striking feature of trench fever is its tendency to relapses, and during these recurrent relapses the patient should always be kept in bed.

The treatment of the chronic disease consists briefly in attempting to improve the general health and hygienic conditions of the individual with particular attention to rest, exercise, diet and climatic conditions.

Prophylaxis

Prevention of the disease is especially dependent upon efficient delousing. The destruction of the virus on underclothing contaminated by louse excreta is also of great importance.

Exceedingly great care should be taken to completely disinfect all patients as soon as practicable and particularly upon their entering the hospital. Patients on entrance should be carefully bathed and subsequently sponged with alcohol, with the object of removing the virus from the skin. Since both varieties of pediculus humanus, *P. corporis* and *P. capitis*, may convey the disease, careful disinfestation of the hair should be carried out. It must be borne in mind that while a temperature of 55°C. for 30 minutes destroys the louse, *P. humanus*, and its ova, such a temperature does not suffice to destroy the virus of trench fever which may be present upon the underclothing of trench fever patients. For the destruction of the virus of trench fever a temperature of 70°C. of moist heat is sometimes necessary. The clothing of patients upon entrance should be removed and both clothing and blankets, whether or not lice or ova are found upon them, should be carefully sterilized by moist heat at a temperature not below 70°C. for 20 minutes, since it is possible for the virus to be still present on the clothing. In institutions autoclaving is most satisfactory. It should be borne in mind that a man with trench fever may be entirely free from lice at the time that he develops symptoms of the disease.

Those handling the sick and their discarded garments should take special precautions to avoid becoming infested with lice. Louse proof

overalls and rubber gloves are desirable for attendants. It has been shown that the virus of trench fever in excreta of lice may retain its virulence for at least four months. Bed linen before washing may be immersed in a 2 per cent lysol or cresol solution for 20 minutes which destroys the virus.

Trench fever patients should at all times be carefully protected from louse infestation, and inspection of them for lice should be made daily, since it has been shown that sometimes even as late as the 300th day of disease a patient's blood may remain infective and be capable of infecting lice. The patients should be treated in separate wards.

As the urine may contain the virus and be infective, it should be sterilized during the active stages of the disease. Infection with the virus may occur through the conjunctiva and 0.1 milligram of infective louse excreta has produced trench fever when inoculated subcutaneously. Infection probably does not take place by the mouth or by inhalation. Sputum cups should be provided for patients and as the sputum may be infective it should also, if present, be sterilized.

The immunity in relation to the disease is variable and one attack does not necessarily protect. The British Commission showed experimentally that re-infection was possible in two instances, on the 132nd and 198th day after onset.

An eradication of lice results in an eradication of the disease.

Addendum

References to Trench fever have been few in the literature of the past several years and obviously, no serious or extensive outbreak had occurred up to 1942. However, if the extracellular organism found so commonly in the intestine of lice (*R. pediculi*) was pathogenic for man, obviously such a human infection would be very common.

Pechtel (1940) reports a case in Poland in which there was an irregular fever of relapsing type with a periodicity varying between 3–5 days. The case was described as one of Wolhynian—Five day fever. The symptoms had persisted for two months before the patient entered the hospital. After admission there were 5 other spells of fever. The serum agglutinated Proteus X19 up to a titer of 1–160. Sulfapyridine treatment was started two days after the last paroxysm of fever; 15 grains being given in 4 days. It is reported that the symptoms yielded promptly and there was no return of the fever. The sulfonamides have been shown to be ineffective in true Rickettsial infections.

Peña Yañez has treated 8 cases of Five day fever during the Spanish-Civil War by means of tartar emetic. The doses were from 8 to 14 c.c. of a 1% solution, given intravenously each day for 7 days, and if necessary repeated after an interval of a week. Diagnosis was made from the typical temperature curves. In 2, a single course of the drug sufficed for cure. In the third, there was a slight recrudescence which yielded to a second course.

Werner (1940) has reported upon *R. quintana* in lice in Fünftagefieber in Germany in the last world war. In 1940 writing from Buenos Aires

he stated that Ogata has succeeded in cultivating *R. quintana* in the testicles of guinea pigs and has used it in the treatment of cases of cerebral syphilis.

Since February, 1942, a number of outbreaks have been reported in the German armies on the eastern front. Bernsdorf states that beginning in February, 1942, trench fever, which had been regarded as a potential threat only, then suddenly became a serious problem for the medical men. Hospital services were greatly embarrassed by the large number of cases and many of the patients were unfit for duty for as long as two to three months. Early cases were mistaken for anomalous typhus fever. After February its nature began to be recognized from the characteristic clinical features and the relapsing type of fever. The Weil-Felix reaction was stated to be negative in trench fever and he thought rickettsiae are not likely to cause a disease with such pronounced tendency to recurrence. No satisfactory treatment was found. Some 10 other reports of outbreaks have been made by German doctors during 1942 and 1943. Among these are those of Reimer, who observed 95 cases in the summer of 1942. No agglutination or precipitin tests were discovered as aids in the diagnosis which was based on the symptoms and the relapsing type of fever. Kerger reports more than 150 cases in Germany (locality not given). The diagnosis was made from clinical symptoms. Jacobi reported 71 undoubted cases from a hospital in the east, the diagnosis being made from clinical symptoms in which there were relapses of the 5 day type. Pyramidon gave relief from pain in only 9 cases and it did not seem to have any curative action. Sulfapyridine was not of value in curing the disease. Sylla observed 200 cases. He felt there was no doubt about the method of transmission by the louse but he did not feel certain about the causal organism. Typical symptoms with a usually fleeting rash were noted and the duration was from 1 to 6 weeks. Weil-Felix reactions of plus or minus 1 to 100 were not uncommon. Widal titres of 1:200 were not uncommon. Treatment on the whole was unsatisfactory with sulfapyridine but neoarsphenamine and atabrine seemed to be helpful in the early stages. Marie (1943) gives no information of the occurrence of the disease in France but refers to the recent outbreaks of the German army on the eastern front in Poland and Russia and points out that no diagnostic laboratory test has been discovered.

Arneth (1942) in referring to the outbreaks in Poland, Russia, Rumania, Italy, France and Belgium says that Kerger found by the end of the second week there was a leukocytosis with a pronounced Arneth deviation of the neutrophiles to the left. During the fever-free periods the leukocytosis was less pronounced but the deviation to the left was still present. Neutrophilic myelocytes appeared and there was a great increase in the number of the large mononuclears and large lymphocytes. He thinks a qualitative count should be made of the lymphocytes and monocytes and that a more or less pronounced increase in both, especially of the larger forms is of assistance in diagnosis. Bormann (1943) has reported an epidemic among German soldiers in North Russia and suggests that the Besarabia fever present in 1942 might have been trench fever.

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Chapter XXIX

VERRUGA PERUANA AND OROYA FEVER

(*Enfermedad de Carrion, Bartonellosis*)

In Peru, for many years Oroya fever and Verruga peruana have been regarded as different clinical manifestations of the same disease, but there has been considerable difficulty in the demonstration of this fact from scientific data and it is only comparatively recently (from such data) that this has been accomplished.

According to the generally accepted opinion, for many years, the disease verruga peruana in the severe form begins with an initial stage known as the *fiebre grave de Carrion*, which is characterized by a fever which lasts from 15 to 30 days, profound anaemia, prostration, and a high mortality. If the patient does not die in this stage, the fever begins to abate and the eruptive or verruga stage commences. If the eruption is generalized and abundant, then it is stated that the patient is sure to recover. In the chronic or mild form of the disease, which is said to comprise the great proportion of the cases, there is moderate fever of intermittent or remittent character, and pains in the joints are common; more or less anaemia is present. The eruption is said to be the culminating feature in both forms, and it appears under various types which, according to the special characteristics they reveal, are termed "miliary," "nodular," or "mulaire." The nodular form, or verruga peruana, is evidently very rarely a fatal disease when uncomplicated with other infections.

Historical Review.—From remote historical times, the inhabitants of Peru are said to have suffered severely from an obscure disease characterized by fever, anaemia, and a nodular or verrucous eruption upon the skin. Over four centuries ago, during the reign of the Inca, Huayna Capac, thousands of lives were swept away, supposedly from this malady, and in the history of the conquest of Peru by Zarate, published in 1545, it is stated that the disease is more destructive than smallpox and almost as disastrous as the plague itself. Perhaps it at this time was sometimes confused with smallpox, although smallpox is mentioned separately. Later this author mentions that the Portuguese soldiers were afflicted by boils or warts of a very malignant kind, and that not a single person in the army escaped them. De la Vega also relates that during the 16th century a quarter of the invading army of Peru under Francisco Pizarro perished from this disease. It was also referred to in Prescott's "Conquest of Peru."

In 1870 a severe outbreak of fever took place among the workmen building the Central Railway between Lima and Oroya, and it is estimated

that at least 7000 individuals died during the epidemic. At this time, the complaint received the name of "Oroya fever," although it appears that it was not contracted in the town of Oroya itself but lower down on the railway, many of the patients being brought to Oroya, where they died. Bourse reported that all of the engineers superintending the building of the Trans-Andean Railway contracted verruga, and that half of them died of it. Of 40 sailors who had deserted from a British ship and gone to work on the railway, 30 died of the disease in the course of 7 or 8 months. In 1906, out of a force of 2000 men employed in tunnel work for the Central Railway, 200 are known to have died of the disease. It appeared to be only necessary for the workmen to spend a single night in the infected districts in order to contract the malady.

Previous to 1885 there ensued much discussion as to whether Oroya fever and verruga peruana were related to one another, or whether the latter was a distinct disease. On August 27, 1885, Daniel Carrion, a medical student in Lima, and a native of Cerro de Pasco, Peru, (a town situated in the mountains far above the localities in which the disease abounds) attempted to solve this problem by vaccinating both his arms with blood from a verruga nodule. It is related that 21–23 days later he began to suffer from Oroya fever, from which he died 16 days later, or on October 5. From this experiment, the conclusion was drawn by Peruvian physicians that verruga and Oroya fever were only different stages of the same disease, and this is the opinion which has been held generally by them since this time. In honor of Carrion's attempt to throw light on the question, the febrile condition, which has been regarded as the first stage of the malady, is now generally known in Peru as "fiebre de Carrion."

In 1898, the monograph of Ernesto Odriozola appeared, which constituted the most excellent and most comprehensive account of the disease which had been written up to that time.

Especially important contributions have been made in Peru in recent years, many with bibliographies, by Battistini, Rebagliati, Escomel, Mackehenie, Coronado, Hercelles, Sr. and Jr., Weiss, Maldonado, Monge, Ortardo and others. Space prevents a review of these publications in the present article.

Etiology.—Very conflicting opinions have been held by many authors regarding the etiology of the disease and the unity of the two conditions. In 1905, Barton described in the red blood cells of two persons sick with severe malignant fever elements similar in morphology to bacilli. In 1909 he noted the presence of these elements in stained blood specimens in 14 additional cases and expressed the belief that they were protozoa and probably the specific agent of the infection. In 1909, Gastiaburu and Rebagliati observed the bodies described by Barton and stated that they were probably protozoa and might be regarded as the pathogenic organism in Carrion's disease. However, later a large number of writers regarded these bodies as products of cell degeneration or were doubtful regarding their etiological significance (Woodcock, 1921, Bassett Smith, 1909, Wenyon, 1926). In 1913 the Harvard Commission observed and described

in detail these organisms and created the genus *Bartonella* for them and named the organism *Bartonella bacilliformis* in honor of Dr. Barton.

FIG. 222.—Parasites of Oroya fever in stained blood specimen. (Harvard South American Expedition Report.)

Bartonella bacilliformis was also discovered and illustrated in large numbers in the swollen endothelial cells, especially of the lymphatic glands, the spleen and liver, of cases which had died in the febrile stages. Attempts

were made to cultivate this organism on the available bacteriological media of that period, but these attempts were unsuccessful. However, monkeys were successfully inoculated with material from human verruga nodules and these characteristic nodules were reproduced through a long series of these animals. On the other hand, a monkey inoculated intravenously with blood from two human cases of Oroya fever with anaemia, containing large numbers of *Bartonella bacilliformis* in the red cells, did not develop any verrugas, nor were there lesions found in them. All

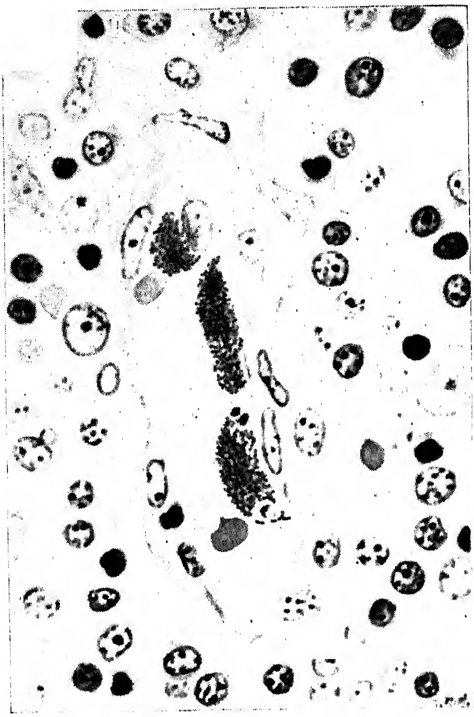


FIG. 223.—*Bartonella bacilliformis* in endothelial cells of lymphatic gland. (Harvard South American Expedition.)

subsequent experiments of this nature with healthy monkeys have likewise failed.

Also, a man who volunteered was inoculated cutaneously with a human verruga nodule and did not develop fever and anaemia or *Bartonella bacilliformis* in the blood, but only a local verruga lesion developed, exactly as occurs in monkeys. The results of such experimental work obviously did not demonstrate or permit the assumption upon a scientific basis that the pathological processes involved in the febrile anaemia or Oroya fever stage and the verruga stage of the disease were identical. Nor did the histological study, with the technique employed at that time, of pathological material from Oroya fever or verruga permit of such a conclusion. Indeed, without the successful cultivation of *Bartonella*

bacilliformis from both the febrile anaemic or Oroya fever stage of the disease and the verruga stage and the reproduction of the characteristic lesions of the disease by such culture, an assumption of this nature upon scientific grounds would have been unjustified.

However, two patients with both anaemia and *Bartonella bacilliformis* in the blood and verrugas also present upon the skin were observed but these were presumed to be concommitant infections, especially since, as in a fatal case of Oroya fever, there were no manifestations of a verrucous eruption either during life or at the autopsy.

Extensive experiments in animal inoculation also conclusively demonstrated that verruga was not caused by a spirochaete or other microorganism of that nature and was not related to the spirochaetal infection known as yaws, in which a granulomatous eruption upon the skin also occurs.

In 1926 the most valuable work regarding the etiology of the affection was performed by Noguchi at the laboratories of the Rockefeller Institute in New York (first in connection with Battistini of Peru). Noguchi by this time had greatly improved his medium for the cultivation of *Leptospira* and protozoa, and carried on studies upon the cultivation of *Bartonella bacilliformis* in New York City, cultures having been prepared from fresh citrated blood taken from a case of Oroya fever and sent to him in New York. Although bacterial contaminations occurred in the original culture tubes during the journey, renewed attempts at cultivation finally yielded a pure culture of *Bartonella bacilliformis* on *Leptospira* media.

Four *Macacus rhesus* monkeys inoculated with cultures intradermally into the eyebrow, and at the same time intravenously, developed at the point of the intradermal inoculation nodules rich in cellular elements and capillary formation. The animals also developed a remittent type of fever. *Bartonella bacilliformis* was found in the red blood corpuscles of these animals in small numbers, and this organism was obtained again from the blood of such monkeys through culture. However, inoculation of the citrated human blood directly into *rhesus* monkeys was without result.

Mayer and Kikuth (1927) made further studies upon a patient with verruga who arrived in Hamburg. In *splenectomized* monkeys they produced nodules by the inoculation of human verruga lesions and in two of these animals there occurred severe anaemia and fever and *Bartonella* in the blood. The direct inoculation of blood containing *Bartonella* or of a papule juice always resulted negatively. However, following Noguchi's technique, they failed to obtain cultures except in one instance, and then only for a second generation, and they suggest that the cultivation of the strains may vary. Kikuth (1931) after Noguchi's lamented death, received a culture from the Rockefeller Institute, but in none of the monkeys which he inoculated with this culture did Oroya fever develop, even after removal of the spleen. However, cultures of *Bartonella bacilliformis* were obtained from verrugas which had been produced in monkeys by the inoculation of the cultures.

The Harvard Commission of 1937 were also able to confirm the cultivation of *Bartonella bacilliformis* on Noguchi's medium from cases both in the febrile Oroya fever stage and in the eruptive verruga stage and to produce verruga lesions in monkeys by the inoculation of such cultures. All attempts to produce fatal Oroya fever in healthy monkeys by the intravenous injection of infected blood failed and in only one monkey that died with tuberculous infection was a mild *Bartonella* infection of the blood noted at necropsy.

In 1921–1924, Mayer observed similar structures in the red blood corpuscles of mice which had been treated with Bayer 204 for trypanosome infection. To these he gave the name of *Bartonella muris*. Later it was shown that the same organism appeared in an anaemic condition following splenectomy in rats. It was thought that this operation had stimulated a latent infection. Other species of *Bartonella* have been described in dogs, monkeys, and guinea pigs (Weinman, 1938) and reports on the cultivation of a number of these organisms have also been made.

Morphology.—In stained and fixed preparation of blood containing *Bartonella bacilliformis* both rod-shaped and rounded forms occur in the red cells. The rod-shaped forms measure approximately from 1 to 2μ in length and from 0.2 to 0.5μ in thickness. They are frequently slightly curved and occur singly or end to end in pairs, or in chains of 3, 4 and 5. When numerous, they often lie parallel to one another. V forms, probably representing dividing organisms, are frequent. Y forms are also not uncommon. The ends of the rods in stained preparations are often more intensely colored. Single rods sometimes show a deep red or purplish granule which may be of the nature of chromatin and which gives the appearance of a swelling at one extremity, the rest of the rod having a more bluish tint, sometimes slightly deeper at the end opposite the one showing the granule. Other rods may be blue throughout or have a deeply stained granule at each end. In organisms occurring in chains the deeply staining granules sometimes give a beaded appearance to the chain.

The rounded forms measure roughly from 0.3 to 1μ in diameter. While many of these are rounded, others are slightly oval, or suggest pear shapes. They occur singly, in pairs, or in groups which suggest previous division.

The red cells may contain a variable number of parasites. In severe infections from 1 to 10 is not unusual. Nucleated red cells, at various stages of development, are of frequent occurrence, and are sometimes infected with the parasites. Rarely *Bartonella* may invade the leucocytes of the blood, as was noted especially by Weinman *et al* in Peru (1937). From the anaemia which occurs in this disease and the number of red cells infected with parasites, it seems evident that the red cells containing the parasites are ultimately destroyed.

Bartonella bacilliformis also occurs often in closely packed masses in the swollen endothelial cells, especially of the lymphatic glands, spleen, liver, and kidneys. In cases which die in the Oroya fever stage, the endothelial cells lining the blood and lymph channels of many organs may be distended with clusters of *Bartonella*. In the endothelial cells of the cutaneous verruga nodules, *Bartonella* was also encountered sometimes in very large numbers but distention of the cells is much less common than is seen in the cells of organs of the Oroya fever cases. *Bartonella* is also encountered in similar lesions produced in monkeys.

Recent Methods of Cultivation and Study.—Pinkerton (1937) has cultivated *Bartonella* in tissue cultures and has found that in early cultures small spherical clusters, 3 to 10μ in diameter, of sharply stained diplobacillary rods appear in the cells. Later, usually by the sixth day, many cells are packed with clusters of less discrete organisms, often coccoid, granular or amorphous, accurately reproducing the picture seen in human lymph-node endothelium from fatal cases of Oroya fever. He found this characteristic pattern in tissue cultures made from the blood from the severe anaemic cases of Oroya fever as well as from cases with cutaneous verrugous nodules.

Weinman and Pinkerton (1938) have recommended for cultivation of *Bartonella* the agar slant modification of the Nigg-Landsteiner-Maitland method recently devised by Zinsser, Wei and Fitzpatrick for the cultivation of rickettsiae. Fresh blood serum

agar has also been employed. On all these media Bartonella grows very scantily and frequently unsatisfactorily.

Jiminez and Buddingh (1940) have obtained a more satisfactory growth and shown the behavior of *B. bacilliformis* in developing chick embryo. More recently Geiman (1941) has described a liquid tryptone-serum medium containing ascorbic acid-glutathione solution and has prepared both semi-solid and solid mediums. On such media relatively rapid and luxuriant growth of *B. bacilliformis* has been obtained in comparison with the results on the older types of media.

Lawkowicz (1938) reported that he had cultivated *Bartonella muris* on Noguchi's medium from the blood of rats. The serum of rabbits, which had been inoculated with cultures of *Bartonella muris*, gave positive Weil-Felix reactions with Proteus O X-19 and O X K and also agglutinated emulsions of *Rickettsia prowazeki*. Several other investigators have failed to cultivate *Bartonella muris*.

Thus Kessler, (1942) has been unable to cultivate *B. muris* by inoculating infected blood directly into the yolk sac into the fertile hens egg. He, however, has shown that *B. muris* can be preserved for at least 11 weeks when the infected defibrinated rat blood is rapidly frozen in a mixture of dry ice and alcohol and then preserved in dry ice.

Howe (1942) has prepared cultures on Geiman's media and by repeated intravenous injections of the living cultures into rabbits, obtained a strongly agglutinating serum. The sera of 5 immunized animals gave positive reactions in titers of 1:160 to 1:640. He then obtained the sera from 6 patients in various stages of bartonellosis and found that their sera agglutinated the organism, however at much lower titers ranging from 1:10 to 1:80. He, nevertheless, regarded these reactions as significant because 13 control sera from healthy persons showed no agglutination of *B. bacilliformis*. The 6 positive sera of the human cases were also tested against Proteus O X-19, O X K and O X-2. Some of these sera agglutinated all 3 of these organisms to some extent, 3 reacted in titers of at least 1:64 and 2 to O X-19, 1 to O X K and 3 to O X-2. He drew no conclusions from these reactions. Highly immunized guinea pigs gave entirely negative reactions to all of these Proteus organisms. (See also page 1011.)

Classification.—There have been several views regarding the classification of *Bartonella*. The genus *Bartonella** was created in 1913 by Tyzzer, Sellards and the writer in connection with the study in Peru of the causative microorganism of Oroya fever and verruga peruana, while the term *Rickettsia* was first applied in 1916 by Rocha Lima to the cellular inclusions observed in the intestines of lice which had fed on patients with typhus fever. Gradually our knowledge regarding these two types of microörganisms has been extended. Some earlier studies suggested that both might be classified in a group intermediate between the protozoa and bacteria. Von Prowazek formerly thought that the *Rickettsia* were probably closely related to the protozoa. How closely either type is related to bacteria is still not entirely clear, but there has been much evidence which has made it appear advisable to separate both, from the true bacteria on the one hand and from the filtrable viruses on the other. It has been generally agreed that bartonellae are not filtrable and only a few of the more minute rickettsiae have been reported to pass through porcelain filters.

The bartonellae and the rickettsiae show certain resemblances from a morphological standpoint. Both are minute or pleomorphic in character and they are Gram-negative and in the human body more characteristically intracellular in nature. However, there is a close association between the red blood corpuscles and *Bartonella* and this is not the case with any *Rickettsia*. Moreover, *Bartonella* are frequently associated with types of anaemia that are not observed in rickettsial infections. The evidence is in favor of the transmission of both *Bartonella* and *Rickettsia* by *Arthropoda*. On the other hand, it is generally agreed that none of the rickettsiae which are regarded as pathogenic have yet been cultivated outside of the body except in tissue culture, while the extracellular cultivation of some of the species of *Bartonella* has already been accomplished. Therefore in this last respect the *Bartonella* may be said to approach nearer bacteria than *Rickettsia*. However, it should be emphasized that the *Bartonella* can ordinarily only be first isolated or cultivated in special media, as Noguchi's leptospiral medium.

* The name *Bartonia* was first given in an article published in the *Jl. A.M.A.* in 1913. The generic name was changed that same year to *Bartonella*. (Harvey lectures 1913–14.)

In some respects they resemble *Bacterium tularense*, another minute organism which is cultivated more easily than the *Bartonella* but which also requires special culture media for its satisfactory cultivation, notably cystine agar or an egg medium made entirely of the yolk. *B. tularense*, like the *Bartonella*, shows a tendency to multiply intracellularly and to form large masses of globi or microorganisms within the endothelial cells.

Epidemiology

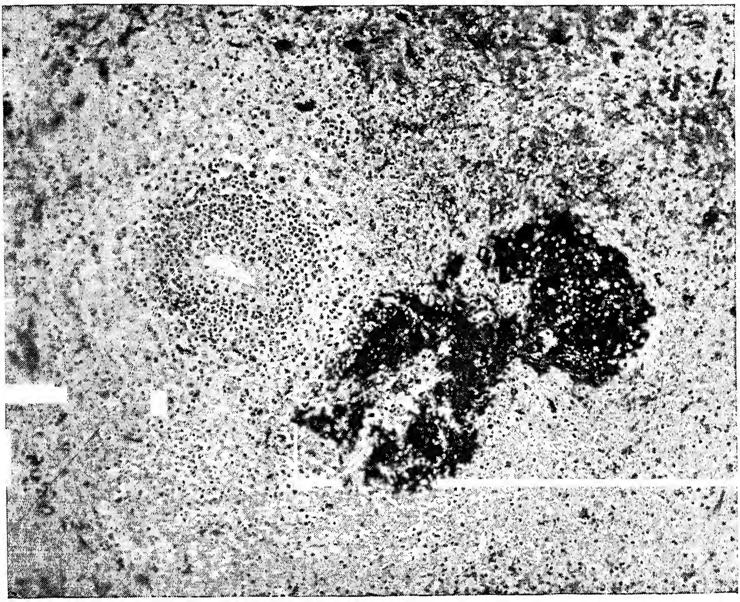
Geographical Distribution.—Verruga peruana has been regarded as a disease peculiar to Peru in that it had not yet been found to originate in man to any extent in any other country of the world. However, recently cases have been discovered in Colombia by Patino-Camargo (1939) and in Ecuador by Montalván & Moral (1940).*

Rebagliati (1940) gives the limits of the geographical distribution in South America as that region of the Andes between 2° north and 13° south. Even within these latitudes the infection is endemic only in the deeply cleft, narrow valleys called *quebradas* formed by elevations of the chains of mountains, and the infection is only endemic at altitudes between 800 and 3000 meters above the sea level. The climate in these valleys is relatively hot in the day-time but cool or cold at night. They are watered by mountain streams and by rainfall. The vegetation is peculiar and scanty, consisting especially of xerophytic or euphorbiaceous types, except where there is direct irrigation from numerous aqueducts led from the river which flows through the valley; here fruit trees are cultured. Insects are prevalent especially *Phlebotomus verrucarum* and *P. noguchi* and *Anopheles pseudopunctipennis* and *A. argyritarsis* and species of *Culex*. The permanent inhabitants are few and most of those who reside in the endemic regions are infected with the disease. In such regions, Rebagliati points out, children are infected in very early years, and those who visit the region for the first time usually become fatally infected if they do not take prophylactic measures. He outlines the geographical distribution in Peru as prevailing in two regions: (1) the Pacific watershed, which includes 21 zones which correspond with equal numbers of hydrographic formations that spring from the western slopes of the Andes and run to the Pacific; and (2) the Marañon watershed, which is the region surrounding the 18 rivers, tributaries of the Amazon.

In Colombia, the disease has been reported by Patino-Camargo (1940) from a jungle region, the Department of Narino, near the Ecuadorian border, and in Ecuador in the Province of Loja, by Montalván and by Moral (1940), near the northern Peruvian border of the disease. In Nariño the disease occurred in severe epidemic form in 1938–39 with a high mortality and under similar ecological conditions to those present in the endemic regions in Peru. It was identified by Patino Camargo as bartonellosis. This fact has been thoroughly confirmed by Groot (1942) and his associates who also found that the serum of the cases showed no agglutination to any of the Proteus organisms or of to typhoid, or paratyphoid bacilli or *Brucella*.

Asymptomatic cases of the disease residing in the Verruga zone have been discovered in Peru. Mackehenie has reported the presence of *Bartonella* in the blood

* Hertig (1940) has isolated *B. bacilliformis* from the blood of a suspected case of the disease in Ecuador. The organism was inoculated into a South American monkey, probably a species of Cebus, in the left eyebrow and left side of the abdomen and verruga peruana nodules developed.



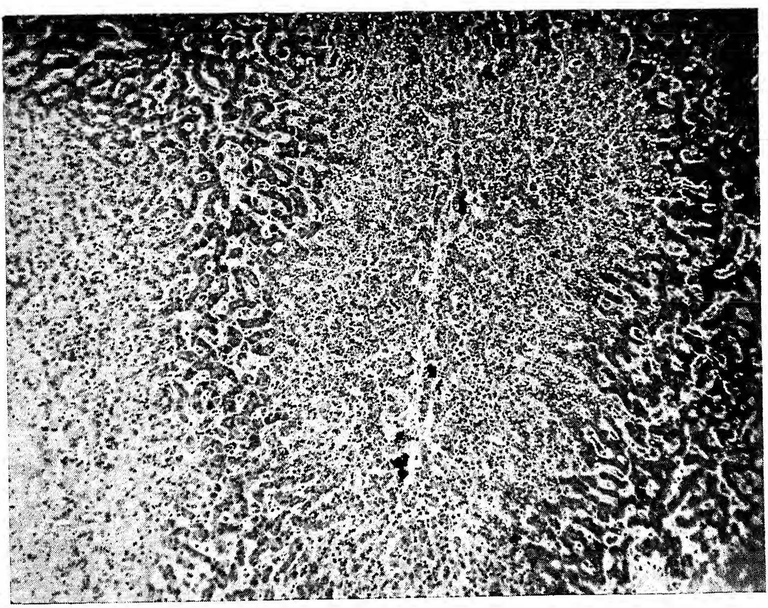


FIG. 224.—1. Oroya fever spleen. Area of necrosis at border of malpighian nodule. × 135. 2. Oroya fever liver, showing area of necrosis, central type. × 100. (Harvard South American Expedition Report.)

of persons not presenting any symptoms and positive cultures of *Bartonella* have been obtained in such cases by Battistini, Weinman, and others. Weinman secured positive blood cultures from 5 persons, in none of whom could *Bartonellae* be found in blood films. Three of the cases had no past history of *Bartonella* infection. The other two gave a history of cutaneous verruga 6 months previously. It is suggested that such cases may constitute an important reservoir of the virus. It seems possible that certain vertebrate animals may play a similar role, but this has not been successfully demonstrated.

Weiss and Pons (1938) have shown the infection of dogs with *Bartonella canis* in Peru, sometimes producing a fatal infection with anaemia. The organism, however, apparently is different from the human one. No cutaneous verrugas were observed. Samper and Montoya (1940) report that in Colombia the common dog was found to be quite susceptible to experimental infection in almost all cases. Many developed verrugae and some died of the disease.

Verruga peruana prevails particularly from January to April, towards the close of the warm, rainy season, when the streams are in flood and the temperature is high and moist, and when insect life is abundant and malaria also prevails. Enteric fevers, and especially paratyphoid and malaria, are very common in the localities where Oroya fever is endemic.

Transmission.—Townsend, in 1913, conjectured that the insect vector was a sandfly. Further evidence incriminating *P. Noguchii* and *P. verrucarum* was obtained by Noguchi, Shannon, Tilden and Tyler in 1929. And Battistini (1931) reported that the bite of *Phlebotomus* can produce infections in the monkey. Two monkeys inoculated with crushed flies developed lesions, and he reported cultures of *Bartonella* from *Phlebotomus*. Hertig (1937) also demonstrated that in sections of *Phlebotomus verrucarum* and *Phlebotomus noguchi*, fed on Oroya fever cases, the Bartonella-like organisms may be present in the lumen and on the surface of the midintestine without, however, any invasion of the epithelial cells. No definite transmitting experiments to man with the living insect have so far been accomplished. However, in his transmission experiments with wild sandflies, Hertig succeeded in infecting 5 of 8 monkeys. He also observed an organism resembling *B. bacilliformis* in the proboscis of certain sandflies. Hertig (1942) in further investigations has found massive infections of the tip of the proboscis of *Phlebotomus* with a minute rodlike or coccoid organism. They have been found in both males and females of three species of the flies from the Peruvian Verruga zone. Over 300 such infections have been observed. The proportion of sand-flies infected was frequently as high as 40 or 50%. The character of the proboscis infection, as to microscopic appearance, intensity and distribution on the mouth parts, was remarkably constant and apparently bore no relation to species, sex, age, or the presence or absence of a blood meal.

The source of proboscis infections, he states, is unknown. Its occurrence in male flies, which do not suck blood, and in females, which have never had a blood meal, indicates that the infection is probably acquired when sand-flies seek other sources of liquids. Out of about 300 uncontaminated cultures of the proboscis, *B. bacilliformis* has been recovered twice, and an un-named micro-organism of similar morphology, about 30 times. There was some difficulty in the primary culture of the proboscis organisms since about half of the uncontaminated cultures yielded no growth whatsoever. He concludes, that the data thus far are insufficient to make clear the extent to which Bartonella enters into these infections, and whether or not they represent the mechanism of transmission of Carrion's Disease. Hertig has been carrying on these studies since 1937 and his most important work should be read by all interested in the subject. Brumpt spent 10 days in Nariño in 1939. Among Phlebotomus, he collected and took back to Paris for classification were specimens of 5 different species, two of which had not been described. Brumpt reported no attempts at experimental infection and it is not known whether these species bite man. He says none of the species which had been found in Peru were encountered in Colombia.

Considerable other evidence has been obtained of the transmission of other species of *Bartonella* by Arthropoda. Transmission of *Bartonella canis* is known to occur through the dog flea (*Ctenocephalus*), (Kikuth); and *Bartonella muris* by the rat louse (*Haematopinus*), (Mayer); and rat flea (*Xenopsyla cheopis*). The transmission by the rat louse (*Polyplax serrata*) was first shown in the United States by Cannon and McClelland (1938).

Pathology

In cases which have died in the Oroya fever stage, at autopsy the skin often shows the pale, yellowish, waxy hue of pernicious anaemia. The lymphatic glands are usually somewhat enlarged and may be oedematous. The heart muscle may be flabby and ecchymoses may be present in the pericardium. The spleen is enlarged. It may show numerous infarctions, and contain large amounts of pigment in the form of yellowish masses or granules deposited between the splenic cells and in the endothelial leucocytes. This pigment is like melanin in not giving the iron reaction. The liver, likewise, is enlarged, infarctions may be present, and areas of toxic degeneration may occur and contain moderate amounts of pigment. The femoral marrow is soft and dark red. Microscopically, the endothelial cells of the lymphatics distended with the causative organisms were particularly noted by the Harvard Commission of 1913. *Bartonella bacilliformis* is found in the red cells, and in addition particularly in the cells of the reticular endothelial system. The vascular endothelial cells, especially of the lymph glands, spleen, liver, and sometimes of the kidneys, are often invaded with clusters of organisms.

Microscopical examination of the cutaneous lesions present in the verruga stage show that the lymphatic channels are often obstructed by a cellular exudate and around such lymphatics, plasma cells, and fibroblasts are encountered. There is marked dilitation of the capillary blood vessels. The structure of the nodules is granulomatous and very vascular, in places almost cavernous, hence the tendency to haemorrhage. The early lesions consist of newly formed blood vessels lying in an oedematous connective tissue. The endothelial cells lining them may be proliferated and in more than one layer. Around these blood vessels there are aggregations of angioblasts which show frequent mitotic figures. The lesions in the early stages are particularly haemangiomatous in character. Later they may show a resemblance to fibrosarcoma. Especially in tissues prepared by Regaud's fixation followed by staining with Giemsa, *Bartonella* are often demonstrable in the endothelial cells of the verrugas, though these cells in the verrugas are not distended with the microorganisms as commonly as they are in the endothelial cells of fatal cases of Oroya fever.

Symptomatology

Verruga peruana, or *Enfermedad de Carrion*, may include two very different clinical syndromes: (1) a severe, often fatal, febrile anaemia (Oroya fever), and (2) a cutaneous, verrucous eruption of haemangioma-like nodules (verruga peruana).

Oroya Fever Stage

The incubation period is usually given as about 3 weeks (16–22 days, Escomel, 1938), and the onset of the disease is marked by malaise and apathy, to be followed by a rapidly developing anaemia, of the pernicious

anaemia type, with an irregular fever of a remittent character fluctuating between 100° and 102°F. and only exceptionally going up to 104°F. Pains in the head, joints, and bones are common. The tenderness over the bones is apparently associated with the marked changes in the bone marrow and may be particularly marked over the sternum.

The patient rapidly develops a very severe anaemia and death results in 20 to 40 per cent of cases in 2 or 3 weeks. Delirium is often noted. The spleen and the lymphatic glands are somewhat enlarged. Associated with the profound anaemia there may be oedema of the legs and about the joints, and functional cardiac murmurs. The kidneys are not generally seriously affected, although albumin is apt to be found in the urine. There may be a diarrhoea in the later stages of the disease. There is no eruption in the severe febrile stage. In severe cases, various manifestations of haemorrhagic character, as petechial spots and bleeding from the gums have been recorded.

The most important findings in the disease are those in connection with the blood examination. The rod-shaped organisms, which are believed to be the cause of the disease, are difficult to observe in fresh blood preparations. They may show definite motility within the red cells, particularly after warming the blood slide. In Romanowsky-stained preparations, the 1 to 2 micron-long rods within the red cells may occur singly or in numbers of 4 or 5. V shapes are frequently seen. The rods show a bluish staining with a deep purplish-red chromatin-stained granule at one extremity. Rounded, oval, or pear-shaped forms may also be seen. While the parasites are present in great numbers in severe cases, they may be very scarce in mild forms of the disease. Noguchi considered the making of cultures superior in diagnosis to the examination of stained smears.

Blood.—*Bartonella bacilliformis* may produce in man an anaemia of the greatest intensity and rapidity. The haemoglobin may be reduced within 2 weeks to 20–30 per cent and the red cells number 1,000,000 to 2,000,000, sometimes less than 1,000,000, with the color index usually greater than 1. The anaemia is usually macrocytic in type, while anisocytosis and poikilocytosis are marked features. Reticulocytes, normoblasts, erythroblasts and megaloblasts may be numerous in the peripheral blood. The bone marrow is hyperplastic, the reaction being of megaloblastic type. In severe infections over 90 per cent of the red blood corpuscles may be parasitized. The leucocytes are usually increased and may number about 20,000, of which 60 to 70 per cent are neutrophiles. Immature neutrophiles, as the metamyelocyte, are very common.

If the individual does not die in this anaemic stage within a few weeks, a gradual improvement in the constitutional symptoms takes place and then frequently an eruptive or verrucous stage follows which is characterized by the appearance of papules or subcutaneous granulomatous nodules.

Ribeyro states that in the clinical evolution of the disease there are benign cases—irregular febrile periods, accompanied by variable phenomena, generally painful, and a certain degree of anaemia which ends

with a more or less general eruption of verruga—and acute cases, in which there dominates an intense anaemia with poorly defined febrile reaction, usually ending with the death of the patient (syndrome of Carrion or Oroya fever); those who escape death present also verruga eruptions. Between these two clinical extremes there are a series of intermediate cases, varying in quantity, quality, and duration of the symptoms, which gives to every patient an individual clinical aspect. All types of cases are met with, from the simple afebrile case of verruga with cutaneous lesions to the fulminating pernicious anaemia type. In less marked cases of Oroya fever, we have the onset of verruga lesions during convalescence. Persons who have had either Oroya fever or verruga are said to remain immune to both.

FIG. 225.—Verruga Peruana. General distribution of nodular lesions. (Harvard South American Expedition Report.)

Verruga Peruana Stage

Verruga peruana is an infectious eruptive disease, lasting 2 or 3 months, and characterized by successive eruptions exhibiting 2 types of lesion,—the miliary and the nodular—both of which show a pronounced tendency to haemorrhage and sometimes to ulceration.

The period of incubation is often indefinite and has been said to vary between 30 and 60 days. Kuczynski (1938) who inoculated himself on the arm with several cultures of *Bartonella* experienced symptoms of marked asthenia, articular pains, and a fever which reached 40°C., such symptoms beginning 17 days after the inoculation, and followed shortly afterwards by the development of 2 large verrugas on the forearm and a series of small ones of the miliary type upon the forehead, eyelids, and legs.

The onset of this stage of the disease may be characterized by rather severe pains of the joints, especially the knees, ankles and wrists, together with a fever sometimes reaching 104°F., but usually not above 100°F., or

the fever may not be noticed. Following the eruption, the temperature usually subsides to normal in a few days. The eruption shows 2 types, the one with numerous, small, wart-like lesions, not exceeding the size of a small pea (2 to 5 mm.)—the miliary type, and the other, with less numerous but much larger, nodular masses—the nodular type. The latter type is more rarely seen than the former.

The Miliary Type.—The eruption is most abundant on the face and extensor surfaces of the extremities and less common on the trunk. In this type, a pink macule appears which rapidly takes on a bright red color and becomes nodular. These nodules may be flat or somewhat pedunculated and bleed easily. At first smooth and shiny, it later on shrivels up without leaving a scar. This form of the eruption may involve the mucous membranes, as of conjunctivae, nose, pharynx, etc. In children the disease is usually of a mild type.

The Nodular Type.—The nodular eruption develops slowly and the lesions may become as large as a pigeon's egg. They tend to become strangulated and then show as ulcerating, fungating masses which are a source of danger from haemorrhage, (Mulaire lesions). The nodular eruption does not invade mucous membranes and is usually confined to the regions of the joints, as flexures of the elbows, knees, etc. The eruptions tend to come out in crops and the duration of the disease extends over 2 or 3 months. The nodules are formed by the proliferation of the endothelial cells of the vessels, angioblasts, many of which have become obstructed with inflammatory exudates consisting especially of plasma cells and fibroblasts.

General Considerations

In none of the lower animals in which *Bartonella* infection has been reported has a verrucous stage of the disease been observed, and the presence of verruga lesions has never been observed at autopsy in any of these animals. The writer still inclines to the opinion that in man, just as in animals, *Bartonella* infection may sometimes pursue its entire course without the appearance of a verrucous eruption and either terminate in death or recovery. That the former is true seems to be generally agreed. However, apparently the traditional view in Peru until recently was still to the effect that if the patient is to recover the verruga eruption, either scanty or profuse, must occur. Tyzzer, who has especially studied the organism in the red cells of the field vole, in a paper published with Weinman (1939) has proposed that the organism in the mouse described by Mayer (1921) and the one in the vole should both be classified in the genus Haemobartonella, indicating that both are found only in red blood corpuscles and not in other cells as is *B. bacilliformis*. This brings up again the question of whether one species of *Bartonella* produces only Oroya fever and a second one a milder type of infection, with a verrucous eruption.

Napier (1939) points out that if this differentiation applies in the case of *Bartonella* infection in man another explanation for the variations in symptomatology can be given, namely that each infection may vary in the

genera represented and that one or more strains of each genus might be present.

An exception to the traditional view has been found in a recent article by the Peruvian physician, E. Escomel (1938) who, under the heading "*Bartonellose fruste*," relates a case with low grade anaemia and fever with *Bartonella* in the blood, in which, after treatment, the fever and *Bartonella* disappeared without the appearance of any eruption, to Escomel's great astonishment. Escomel also, in a discussion of *Bartonella bacilliformis*, the "agent causal," refers to the fact that the histoid or eruptive stage may be macroscopic or microscopic, but he does not say whether the microscopic eruptive lesions were detected during life, nor does he describe them in such connection.

Mackehenie has reported the presence of *Bartonella* in the blood of persons not presenting any symptoms of the malady, and Battistini, Weinman and Hurtado (1938), have secured cultures of *Bartonella* from the blood of apparently healthy individuals living in the verruga zones.

Pittaluga (1938) who has studied Bartonella infections in rats and in dogs points out that human Bartonella infection is not comparable in its evolution with the infection of animals caused by *B. muris* and *B. canis*, or to the disease in monkeys caused by the injection by *B. baccilliformis* and that the last organism should be separated from other members of the group.

Weiss, of Lima (1927–1928), in an important and interesting article, suggested that at the termination of the Oroya fever or haematic phase the virus becomes fixed in the tissues and the histoid reticulo-endothelial reaction so produced leads, after a varying interval, to the production of the verruga nodules. Thus the formation of the verruga nodules by the proliferated reaction of the angioblastic or reticulo-endothelial cells partakes of the character of an allergic reaction. In the second histoid phase, there may be a reaction either with or without eruption.

Howe (1943) has carried out extensive *immunologic studies* in regard to the disease with special reference to the agglutination tests. He reports that a measurable titer of agglutinins is probably not produced in all persons with Carrion's disease. On the other hand, it appears that agglutinins, when they do occur, are detectable most often during the early acute anaemic stage (clinical or subclinical Oroya fever), when blood cultures are regularly positive for *B. bacilliformis* and the parasite is often detectable in the blood smear. From observations made on several patients, at different stages of the disease it seemed probable that the titer of agglutinins rises and most often reaches a peak just prior to the appearance of the eruption. In the majority of cases in which eruptions occurred, there was apparently a decline in titer as the eruption progresses and finally subsides. In the majority after all evidence of eruption had subsided, no agglutinins were found in the serum. In many instances blood cultures positive for *B. bacilliformis* persisted longer than a positive agglutination test. He thought it unlikely that agglutins play any major part in the almost universal acquired immunity which he thought followed the typical clinical disease or in the apparent immunity which might be present in long term residents of endemic centers, who deny past history of the infection. Nonimmune persons who had received formaldehyde-treated vaccine developed agglutinins but apparently these agglutinins did not prevent an asymptomatic infection from occurring when such persons were exposed to the disease in an endemic region as cultures made from their blood revealed the presence of *B. bacilliformis*.

Also, he reports it is evident that administration of specific hyperimmune rabbit serum of high agglutinin titer does not sterilize the blood stream completely in cases of severe Oroya fever. The agglutination test did not seem to be of great use, either in determining past infection or in estimating the degree of immunity in persons who claimed to have had Carrion's disease. In the majority of the cases it did not occur in dilutions beyond 1:20; in 4 cases it occurred in a dilution of 1:160. Howe says that even in the lowest dilutions of serum the test is thought to be of diagnostic significance.

Complications and Prognosis.—The disease is frequently complicated with malaria. Paratyphoid fever has also been a common complication, and Rebeyro believes that when this infection coexists, the prognosis is rendered much more unfavorable. The very severe febrile anaemic cases usually result fatally. Those with verrucous eruptions frequently show few unfavorable symptoms and are very rarely fatal, unless complicated by other infections.

In children the disease is often mild. Latent forms of infection without apparent symptoms have been shown to exist.

Mera (1943) has summarized the present knowledge of the subject and some of the investigations performed recently by Peruvian and Colombian physicians.

Treatment

Treatment which has been found successful for other macrocytic anaemias, as pernicious anaemia, tropical nutritional anaemia, and sprue, is not effective in *Bartonella* infection in man, as might be expected, since the former are deficiency diseases and the latter an infectious one. Kuezynski (1937) believed that vitamins, and especially vitamin B_1 produced a favorable effect on the infection. There have been a number of reports of the efficacy of the administration of iron and copper in the infectious anaemia of rats which develops after splenectomy. Perla and Gottesman have reported that when the animals are fed iron and copper before the removal of the spleen, *Bartonella* infection does not develop. Perla believes splenectomy causes increased elimination of copper and states that animals on a normal diet do not receive enough copper to prevent the development of the infection after the spleen is removed. It is also stated that neosalvarsan, administered before splenectomy, prevents the development of the anaemia in rats and if administered after the development, it has a marked effect. In the treatment of infectious anaemia of dogs, which anaemia, however, is seldom severe (in at least some localities) and death is infrequent, neosalvarsan is said by Kikuth to exercise a specific effect. However, this is not the case in human *Bartonella* infections. It has been conclusively shown by a number of Peruvian physicians that the most severe anaemic cases usually result fatally in spite of such treatment. Kikuth has recently (1937 and 1938) written of the value of an arsenic antimony compound, designated as S.D.T. 386B, which contains 18 per cent of arsenic and 20 per cent of antimony, a brown powder, readily soluble in water. It is stated that the lethal dose for rats is 750 mgm. per kilogram and the well tolerated dose 500 mgm. per kilogram. In heavy *Bartonella* infections in rats, 0.2 mgm. per kilogram is said to be effective and to have a specific action. Kikuth further states that Manrique has obtained noteworthy results in the treatment of 14 cases of Oroya fever in Peru, for which he admits hitherto there has been no treatment other than symptomatic. Doses of 0.1 to 0.3 grams, repeated two or three times, brought about disappearance of *Bartonella* from the circulating blood and initiated an increase in the erythrocyte count and a rapid improvement in the general conditions.

However, the general opinion among a number of the most conservative Peruvian physicians today is that the severe infections have not been favorably influenced to any great extent by this drug or any other drug treatment, or by transfusion of normal blood. Cases which we observed treated with this compound, 386B and other antimony compounds, were not noticeably favorably affected. Such drugs were employed in three of the cases we observed which resulted fatally. Ribeyro (1940) at the conclusion of his monograph states there is no specific therapeutic treatment for this disease. Treatment should be designed to building and strengthening the resistance of the patient who is suffering with the syndrome of Carrion and an attempt should be made to supply the organic elements that have been destroyed, to foster blood regeneration and to excite at the proper moment in the evolution of the disease, the defensive functions of the reticulo-endothelial system. Hence the successful treatment of severe *Bartonella* anaemia in man would appear to be still an unsolved problem.

In the treatment of cutaneous verrugas, the ordinary principles of cleanliness apply to the care of the lesions to prevent secondary infections. When the large tumor-like masses begin to ulcerate or become gangrenous, some advise that they should be excised. It must be remembered that dangerous bleeding may occur at unexpected times.

Howe has prepared an immune serum of high agglutinin titer in rabbits by the intravenous administration of large amounts of *B. bacilliformis*, both in the fresh and in the formaldehyde-treated state. The titer was usually 1:2560. Three cases of severe Oroya fever were treated. A man of 51, another of 21 and a lad of 15 years. The first had 10 cc. daily intravenously, on the 20th–24th days of the disease having 50 cc. in all. The man of 21 had on the 21st and 26th days of illness, 100 cc. and 150 cc. transfusions of whole blood (the donors had never had Carrion's disease), and from the 23rd to the 27th days, 10 cc. doses daily of the immune serum. The boy of 15 had a total of 60 cc., namely 10 cc. on the 8th, 10th, 12th, 13th, 14th and 17th days of illness. In none of the three was there any very definite change in the clinical picture as a result of the serum therapy. However, in the boy the typical miliary eruption appeared unusually early, on the 14th day of illness. Whether there were any indications of serum sickness is not stated. In all three there followed, shortly after the injections began, an appreciable diminution in the percentage of erythrocytes infected with *B. bacilliformis* as determined by examination of blood films and Howe thought that the reduction appeared to be more gradual in other cases which had not received immune serum. He also noted that in these 3 cases a diminution occurred in the number of colonies of the organisms obtained in cultures taken during the time the treatment occurred. The type of colonies obtained in cultures taken before and after administration of serum indicated a change from finely granular and diffuse growth to a coarse and sparsely scattered type of growth. These changes were retained in transfers from original blood cultures and their significance is not clear. It remains to be determined whether the change in the number of infected corpuscles was merely coincidental with or was

directly consequent on the injections though this suggested that the serum had some effect in clearing the organisms from the blood stream.

Prophylaxis

Prophylaxis consists of avoiding the endemic districts after nightfall. If one is compelled to remain in them he should protect himself after sundown beneath a mosquito-net with a fine mesh, or be in a screen-proof room. It may be recalled that Shannon, while studying the epidemiological conditions and the question of transmission and while collecting insects, lived for over 4 months in the endemic zones. Nevertheless, by exercising such precautions he protected himself from infection.

It is difficult to find or to eradicate the breeding places of *Phlebotomus* in the endemic zones.

Human cases of the disease, either active or as latent infections, constitute reservoirs of infection in such regions.

Prophylactic Immunization

Howe and Hertig (1943) report that a group of 22 guards without previous history of Carrion's disease were inoculated subcutaneously with 1 ml. of formalized Bartonella vaccine prior to being stationed in the verruga zone. Most of them received 1 or 2 more injections during the first 2 weeks of their service. The majority of them were examined by the authors during the ensuing 7 months, blood for cultures and serum being taken from each guard on several occasions. The subcutaneous inoculation of the vaccine resulted in the appearance of agglutinins in their serum. From the blood of 12 or 55%, *B. bacilliformis* was cultured on one or more occasions, during the time they were in the verruga zone, subsequent to their inoculation with the vaccine. The authors thought their results seemed to show that active immunization as they carried it out, although not preventing infection may definitely ameliorate the course of the disease. Five out of the 12 developed a mild eruption and all 12 had shorter or longer periods of mild systemic infections.

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SECTION IV

NUTRITIONAL DISORDERS

The study of the deficiency diseases since the last edition of this book has become a specialty. Also, the literature upon the subject is now so vast that recently several special text books relating to the vitamins have been published.

Dr. George C. Shattuck for a number of years has been devoting special study to the deficiency diseases and he has kindly agreed to summarize our modern ideas on the subjects discussed in this section.

Chapter XXX

MALNUTRITION; NUTRITIONAL OEDEMA; EPIDEMIC DROPSY

Introduction.—The distribution of most of the nutritional disorders is world wide. Only those which are particularly common in the Tropics or sub-Tropics will be described in this Section.

With regard to the vitamin deficiencies, Mackie (1940) has emphasized important concepts based upon the newer knowledge of this subject. He said: "Various of the vitamins have been shown to be the active or prosthetic fractions of enzymes which are essential for the breakdown of foodstuff in intracellular metabolism." In the earlier stages, there is disturbance of function only. If the process advances far enough, demonstrable anatomical lesions appear. Thus, the estimated incidence of nutritional deficiencies will depend upon whether or not early signs of deficiency have been accepted as criteria for diagnosis.

Several observers have pointed out that vitamin deficiency may be associated with dysfunction of the digestive glands or with disorders of some of the glands of internal secretion.

There are grounds for believing that deficiency of certain vitamins may lower the threshold of resistance to bacterial infection and, perhaps also, to virus infections and metallic poisons which attack the nervous system.

A key to the recent literature on the vitamins can be found in the series of authoritative articles first published in the Journal of the American Medical Association under the auspices of the Council on Pharmacy and Chemistry and the Council on Foods of the American Medical Asso-

ciation and subsequently brought together in book form as "The Vitamins" 1939. Each of these articles includes a comprehensive reference list. "New and Nonofficial Remedies," published yearly by the American Medical Association, provides pharmaceutic information and defines "allowable claims" for vitamin preparations. The "Tropical Diseases Bulletin" reviews periodically, most of the important literature bearing on nutritional diseases of the Tropics. In "The Avitaminoses" by Eddy and Dalldorf (1938), the more important original sources are listed at the end of each chapter.

In their book entitled "Vitamin B-1 (Thiamin) and Its Use in Medicine," R. R. Williams and T. D. Spies have evaluated current knowledge of beriberi and allied nutritional disorders, up to 1938.

In a monograph published by Dr. León De Soldati, Buenos Aires, Argentina, 1940, entitled "Los Trastornos Circulatorios de la Avitaminosis B-1," he has discussed in detail the circulatory disorders resulting from deficiency of Vitamin B-1 in man and in animals.

Deficiency of Vitamin D, which manifests itself in children as rickets and in adults as osteomalacia, has seldom been observed in the Tropics. There have been a few cases of "rickets" reported from Puerto Rico, but there is reason to believe that most of these diagnoses were erroneous.

Anaemia, mild or severe, is widespread in the Tropics. Malaria, ancylostomiasis, sprue, and scurvy account for a large proportion of the anaemias. Most of them are hypochromic or microcytic in character and they usually respond well to iron. The anaemia of malaria is attributed chiefly to blood destruction and that of ancylostomiasis to chronic blood loss. In either case, there is a deficiency of iron. The anaemia in sprue and allied deficiency syndromes results from deficiency or absence of the extrinsic or of the intrinsic factor of Castle or from a deficiency of both factors. These anaemias require liver extract for their cure. In scurvy, the anaemia has been traced to deficient production of erythrocytes by the bone marrow. The response to administration of vitamin C is dramatic.

"Pathological Physiology and Clinical Description of the Anaemias" by W. B. Castle and G. R. Minot (1936) contains much information relating to the nutritional anaemias of the Tropics. The milder grades of anaemia are often associated with malnutrition or attributable to one or more of a great variety of disorders.

Malnutrition

Definition.—By the term "malnutrition" is meant a condition of suboptimal nutrition which may or may not be associated with recognizable signs of any well defined deficiency syndrome. The weight-to-height ratio, or some other index of the level of nutrition, may be useful for the recognition of malnutrition in a borderline case. Such indices are of limited value, however, because they vary considerably within normal limits, because water retention may occur with or without oedema, and because certain deficiency syndromes are not necessarily associated

with loss of weight. Bigwood* (1939) has described and discussed the methods of making nutritional surveys and of recognizing malnutrition in individuals.

Incidence.—Malnutrition is very common in many of the indigenous races of the Tropics. Among the common causes of malnutrition in these groups are periodic or permanent scarcity of food, chronic or recurring diseases, loss of teeth, and dislocation of habitual modes of life incidental to modern progress. The nutrition of individuals of the white race, residing temporarily in the Tropics, suffers in many instances from failure to eat the fresh fruits and vegetables which are obtainable locally, from other unhygienic habits, or from disease.

ETIOLOGY

Food which has been ingested remains, physiologically, outside the body until it has been absorbed. Probably, some of the disorders of metabolism which are not dependent primarily on malnutrition, may interfere with the utilization of essential food factors even after absorption from the intestines has taken place. Thus, nutrition depends first on ingestion of adequate amounts of all essential food factors; second, on their absorption in sufficient amounts; and third, on their efficient utilization by the tissue cells of the body.

Some of the recognized "food deficiency syndromes" are traceable to lack of specific substances. Among such are certain minerals, proteins, and the known vitamins. Other symptoms are curable by means of unknown substances contained in liver. Frequently, in individual cases two or several essential food factors may be insufficiently available. The patient may then exhibit a combination of symptoms which does not fit into any of the well known deficiency syndromes.

TREATMENT

Treatment of malnutrition requires recognition and removal, when possible, of the underlying cause. This may involve improvement in diet or in living conditions, adequate rest and, perhaps, specific medication for anaemia or for vitamin deficiency, or treatment of some concomitant disease.

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Nutritional Oedema and Epidemic Dropsy

Synonyms.—Acute Anaemic Dropsy, War Oedema, Famine Oedema, Prison Oedema, (?) Epidemic Dropsy.*

Definition.—Nutritional oedema is generally attributed to deficiency of protein in the diet. Recently published textbooks have thrown together nutritional oedema and epidemic dropsy. The descriptions of many cases of epidemic dropsy seen in India indicate that this disease is often associated with skin lesions which are not seen in ordinary cases of nutritional oedema. Therefore, one may doubt the identity of the Indian form of epidemic dropsy and nutritional oedema.

Incidence.—Local outbreaks of nutritional oedema or of epidemic dropsy have been reported from India, Mauritius and Fiji; from Tennessee (Youmans: 1932); and from Spain during the recent civil war (Jour. Amer. Med. Assoc.: 1939). Nutritional oedema has been prevalent, at times, in Java and among prisoners in Haiti. It was common in Central Europe as a result of semi-starvation during the World War. In India, epidemic dropsy is seen especially during the rainy season or subsequently, when the weather is "cold." Outbreaks do not occur every year. Probably, sporadic cases of nutritional oedema may be found almost anywhere. Doubtless, there are cases in which oedema of nutritional origin is associated with deficiency of various other food factors.

ETIOLOGY

Youmans et al (1932) studied 12 cases of mild nutritional oedema. They stated that in all but one of their cases the total caloric value of the food ingested was below basal requirements; that the average protein intake ranged from 20 to 52 Gm. daily. In 8 of their cases, it was below the usual minimum of 0.5 to 0.7 Gm. per kilogram of body weight. In a subsequent report (1933) on 31 patients, they found that the total proteins were usually normal, the serum albumin slightly or moderately reduced, and the globulin normal or increased. Calculated colloid osmotic pressures (using Govaert's factors) were slightly or moderately below normal in the majority of patients with oedema. When the protein in the diet was increased, the albumin tended to rise gradually and the oedema to disappear. It was believed that reduction in the serum albumin was especially significant but that other factors, such as intake of water and salt and, perhaps, a nutritional injury to the endothelium of the capillaries, might be factors of secondary importance. The normal range of serum proteins was considered to be as follows: total protein 6.5 to 8.5 per cent; albumin 4.2 to 5.7 per cent and globulin 1.3 to 3.0 per cent.

Reduced specific gravity of blood serum has been reported (Pasricha, Lal and Malik: 1938).

* One form of epidemic dropsy is now attributed to poisoning by an adulterant of mustard oil. See page 1210.)

The main factors which can enter into the production of oedema have been discussed in detail by Peters (1935) and presented briefly by Landis (1935). Experiments by Lepore (1932) on dogs, show that increased intake of fluid and of sodium chloride hasten the development of oedema. With regard to his work on "toxemia" in pregnancy, Strauss (1937) said: "The evidence presented suggests that the manifestations of 'toxemia' of pregnancy in the patients studied resulted from water retention conditional upon hypoproteinemia" and that "The administration of sodium is dangerous in pregnant women with hypoproteinemia." He said that sodium bicarbonate and sodium chloride are equally detrimental. Subsequently, Strauss and Fox (1940) reported that anaemia *per se* appears to be a cause of water retention and that the retention after administration of sodium chloride is inversely proportional to the haemoglobin level. Weiss and Wilkins (1936), after studying cardiovascular disturbances in vitamin B-1 deficiency, stated that the oedema observed in their cases could not always be explained either by the degree of circulatory failure or by lowered osmotic pressure of the blood plasma. This observation is difficult to interpret. Vedder (1940) has attributed the oedema of wet beriberi to embarrassment of the right ventricle alone.

Elliott (1933) said that "Depletion of serum protein occurs clinically as a result of protein restriction in diet, protein waste as in albuminuria, or as a result of disturbed metabolic processes," and that "when serum proteins are depleted below a level of 3 or 4 Grams per cent, oedema may appear." He believed that "Disturbances of the acid-base equilibrium of the serum are probably of *second* importance in determining the state of hydration of the body."

According to Mecray et al. (1937), patients who have peptic ulcer or gastric malignancy often suffer from nutritional defects and, when the dehydration which they so frequently exhibit has been overcome, they may have hypoproteinemia with or without oedema.

Sharp (1935), Carman (1935), and previous observers, have described a supposedly nutritional disease associated with oedema which occurred in Kenya and the Gold Coast. Most, but not all of the cases were in infants. The symptomatology suggests the coexistence of multiple dietary deficiencies.

When "war oedema" appeared in Central Europe, there had been a prolonged dietary shortage of fats, but there may also have been a deficiency of protein in the diet. Mann's (1938) observations on prisoners in Haiti, led him to believe that deprivation of direct exposure to sunlight was an important causative factor in his cases of oedema.

Many cases of "epidemic dropsy," reported from India have exhibited neurologic symptoms suggesting beriberi. This fact seems to show that features of epidemic dropsy and of beriberi may occur together. Outbreaks of dropsy are particularly common among people whose staple diet is husked rice.

The cause of epidemic dropsy in India has been the subject of much study. The infectious theory is losing ground. The view that the disease

is caused by a toxin which has been found in damaged rice has inadequate support. Pure mustard oil is free from any toxic principle but an adulterant of mustard oil (*argemone*) appears to have toxic effects. Some outbreaks of epidemic dropsy have been attributed to this substance. On the other hand, it seems highly probable that many cases of epidemic dropsy are due essentially to disorders of nutrition.

PATHOLOGY

No characteristic lesions of the internal organs have been described. De and Chatterjee (1935) have studied the pathology of epidemic dropsy in India with special reference to the skin. They attributed the erythema to vascular dilatation and the "ecchymotic" patches to telangiectasis. The nodules which were found on the mucosa of the mouth, tongue and nose, as well as on the skin, contained dilated vascular spaces.

Dilatation, especially of the right side of the heart, with thinning of the wall and separation of the muscle fibers by dilated capillaries, somewhat similar changes in the ciliary body of the eye, and evidences of glaucoma were observed in some of the cases. The membranes of the spinal cord and of the peripheral nerves showed marked "vascularity," but there was no degeneration of nerve fibers.

SYMPTOMATOLOGY

The oedema may be slight or pronounced. Generally, it begins in dependent parts. Oedema of the face and anasarca may develop. Associated signs and symptoms are extremely variable. They include increasing emaciation, muscular weakness, irregular fever or subnormal temperature, diarrhoea and vomiting, pleural and pericardial effusions, bradycardia or tachycardia and dyspnoea on exertion, loss of knee jerks and sensitiveness of the calf muscles to pressure, and various ocular lesions. Pregnant women frequently abort.

An intimate relationship between non-inflammatory glaucoma and nutritional oedema has been pointed out repeatedly.

Skin.—In epidemic dropsy, various types of skin lesions have been observed: blotchy, purplish-red erythema which produces pigmentation; vascular nodules or "sarcoids," large or small, which sometimes are pedunculated; small red nodules scattered over the body; an erythematous or petechial rash on the legs; pigmentation of the face and of other exposed parts. The erythema is due to telangiectasis and the vascular nodules are hemangioma. They bleed readily and profusely when damaged (Chopra et al: 1935 and De and Chatterjee: 1935, Ghosh: 1941). The extent of the skin lesions bears no relation to the severity of the illness. The form of epidemic dropsy resulting from the ingestion of argemone oil is discussed on page 1210.

Blood.—The haematologic changes were studied by Chatterjee and Halder (1935). They found little reduction in the erythrocyte count but, sometimes, the haemoglobin was markedly reduced. The leucocyte count was apt to be reduced in the early stages but not subsequently. The lymphocytes and the eosinophiles were relatively increased. "Toxic

cells" were described. They were leucocytes of a peculiar type, exhibiting vacuolization and basophilic granules.

It seems highly probable that the clinical picture in many cases of nutritional oedema depends upon the existence of multiple deficiencies. The cardiac symptoms and the sensitiveness of the calves and the loss of knee jerks are highly suggestive of deficiency of vitamin B-1 and some, at least, of the ocular lesions might be caused by deficiency of vitamin A. The cause of the skin lesions is by no means clear. The anaemia might be caused by iron deficiency.

DIAGNOSIS

Oedema associated with evidence of malnutrition suggests the diagnosis of nutritional oedema. An "epidemic" without neurologic symptoms, which occurs in a labor gang, in a prison, or in a population group, is likely to be caused by a deficiency of protein in the diet. When some of the cases show signs of beriberi or of some other well known food deficiency, there is a high degree of probability that protein deficiency may be a factor in these cases as well as in those showing oedema only. Probably, oedema which may be of nutritional origin occurs in connection with a great variety of diseases in which nutrition is disturbed through inadequacy of the diet, defective utilization of food, or pronounced loss of protein as in chronic nephritis. Decrease of serum albumen, alteration of the albumin-globulin ratio, lowered osmotic pressure or decreased specific gravity of blood-serum, favors a diagnosis of nutritional oedema. The skin lesions, when present, may be of various types.

Prognosis.—Mortality is low, as a rule. Deaths are usually attributed to cardiac decompensation. It seems possible that B-1 deficiency may be the true cause of such deaths.

TREATMENT

The first requirement is a diet rich in protein and vitamins and of high caloric value. When oedema is pronounced, the intake of fluid and of sodium, whether as sodium chloride or sodium bicarbonate, should be restricted. Cardiac symptoms, when they occur, suggest that vitamin B-1 should be administered in adequate dosage.

The skin eruptions of epidemic dropsy are said to respond to a high protein dietary and good results in glaucoma have been attributed to similar methods of treatment.

Haemorrhages from injured nodules may be prolonged and severe. Bleeding must, therefore, be watched for and controlled. Anaemia, when marked, may require treatment with iron or with liver extract. After massive haemorrhage, blood transfusions are indicated. They not only help to restore the cellular elements of the blood and the haemoglobin, but they combat the depletion of serum protein.

Parenteral injections of various proteins have been recommended recently. Their use is still in the experimental stage.

Methods of dealing with hypoproteinemia in postoperative surgical cases have been discussed by Ravdin et al: 1940.

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Chapter XXXI

SPRUE

Synonyms.—Psilosis, Ceylon Sore Mouth, Cochin-China Diarrhoea.

Definition.—Sprue is an afebrile, chronic or relapsing disease characterized by the passage of stools which are voluminous, mushy, the color of putty and, sometimes, frothy. The classical associated symptoms are weakness, emaciation, gastro-intestinal discomfort, changes in the tongue, and anaemia.

Geographical Distribution.—Sprue is common in Whites of European origin who are living or who have lived in southeastern Asia, the East Indies, India, Ceylon, Puerto Rico, or the West Indies. Sprue has been reported less often from other tropical or subtropical countries. Strange to say, sprue seems to be rare in Africa. Sporadic, indigenous cases of non-tropical sprue, have been reported from many parts of the temperate zone, including the United States of America and many of the countries of Europe.

Incidence.—Sprue usually develops in the middle period of life and more often in women than in men. It may appear in childhood. Frequently, it is a sequel of dysentery or of some other debilitating condition. It is commonly associated with pregnancy. The native races of the tropics are far less liable to sprue than are persons of European race residing in the tropics. Even though "sprue houses," in which successive tenants have suffered from this disease, are known in India, it does not follow that any specific infection is operative. In India and in Ceylon, sprue occurs not only in the hot lowlands but also in the mountains at considerable altitudes. "Hill diarrhea" or Simla trot" develop particularly in Europeans resident in India soon after their arrival at a hill-station. Although formerly considered as a separate disease, hill diarrhoea tends now to be regarded as an incipient state of sprue. It is followed not infrequently by typical sprue.

Europeans who have resided in the regions where sprue is common, rather frequently develop the disease after returning to the United States or to Europe. The interval of time varies from a few months to fifteen years or even longer. The past history of many of these cases indicates that they had had dysentery, diarrhoea or recurring gastro-intestinal symptoms before the signs of sprue became characteristic.

Etiology

The etiology of sprue was for many years obscure. Several investigators formerly believed a yeast (*Monilia psilosis*) found in the stools was the cause.

Studies by Castle and his associates (1935) indicate that sprue is fundamentally a deficiency disease having features closely resembling those of Addison's anaemia. According to Vedder (1940), sprue may develop in persons whose diet has been excellent. On the other hand, cases of sprue afford abundant evidence of defective absorption of food. Castle believes (1935: p. 72) "that in sprue, as in pernicious anaemia, there is involved the failure of a reaction between an extrinsic factor in the diet, associated in several substances with vitamin B-2 (G), and an intrinsic factor, present in the gastric contents of the normal person. In addition, difficulty with the absorption of substances from the intestinal tract resulting from this hematopoietic reaction is probably involved in certain instances of both diseases. In different patients with sprue the relative importance of these mechanisms is variable. Sprue with macrocytic anaemia thus arises from the variable participation of three defects: of the extrinsic factor, of the intrinsic factor and of absorption. Dietary deficiency of iron, gastric anacidity and intestinal impermeability may also decrease the normal intake of iron." The "intrinsic factor" of Castle is less frequently lacking in sprue than in Addison's anaemia.

The dietary histories of many, but not of all sprue cases, indicate deficient ingestion of substances containing the "extrinsic factor"; e.g. meat, eggs and whole cereals, a disproportionately large ingestion of carbohydrates and inadequate consumption of fresh vegetables and fruits.

The specific infectious theory of the etiology of sprue, which has had ardent advocates, is no longer tenable. It is by no means clear that yeast-like organisms, which may be found in the faeces, are even of secondary etiologic significance. Infectious diseases, debilitating influences, pregnancy, and many conditions which are associated with disorders of digestion or of assimilation of food, may serve as contributory or conditioning factors.

If sprue is essentially a deficiency disease, indigenous cases might be expected to occur in almost any part of the world, and there would seem to be no ground for recognizing categories based on geography. Probably, the more frequent occurrence of sprue in certain tropical countries is to be attributed to conditioning factors which are not yet fully understood.

Vedder's (1940) analysis of the causation of sprue is of great interest in this connection. He inclines to the belief that sprue develops only in predisposed persons and he suggests that dysfunction of the anterior pituitary gland may be intimately connected with the disturbed absorption from the intestine. Cases which are capable of response to diet are curable by means of a diet rich in the components of vitamin B-2. When the disease does not yield to diet, it is because the necessary constituents of the food are not absorbed. Such cases usually respond to crude liver extracts administered parenterally. These crude extracts are rich in the factors included in vitamin B-2. Vedder pointed out that the fatty diarrhoea of sprue may be expected markedly to reduce the absorption of the fat-soluble vitamins, A, D, K, and that of vitamin B-1 as well. Deficiency of these factors might account for some of the lesions which have

been observed in sprue, but deficiency of the constituents of vitamin B-2 appears to be of special significance.

Pathology

Sprue causes no characteristic pathology. The lesions seen at autopsy are usually indicative of the terminal stage of the disease. The tissues are wasted and dehydrated; fat deposits are extremely depleted; the liver is apt to be much reduced in size; and changes in the bone marrow are similar to those seen in Addison's anaemia and are often pronounced (Castle et al: 1935). Atrophic changes in the pancreas, the kidneys, or brown atrophy of the heart muscle have been observed.

It is believed that the small intestine may become thin-walled, pale and diaphanous as a result of atrophy of the mucosa and fibrosis of the submucosa. "Inflammatory changes" or irritative phenomena may be found in the tongue, oesophagus or small intestine. They may be associated with round-cell infiltration of the intestinal wall or with ulcerations which occasionally lead to perforation. Sometimes, gray mucus is adherent to the surface of the gut and oedema of the intestinal wall has been observed. Enlargement of the mesenteric lymph nodes, pigmentation and fibrosis have been reported. Some of the "lesions" of the mucosa, formerly attributed to sprue, are now regarded as post mortem changes.

Symptomatology

As a rule, the onset is so insidious that it cannot be dated accurately, but the attack may begin acutely with pronounced, watery diarrhoea. There may be fever for a few days. Thereafter, the temperature tends to be subnormal.

The first symptom, and sometimes the only sign noted by the patient, may be sensitiveness of the tongue or of the buccal mucosa, which is manifested especially when an alcoholic beverage or some acid or highly seasoned food is taken. At this time, earlier or later, lassitude, anaemia, mild gastro-intestinal discomfort and morning diarrhoea develop. There may be alternating periods of diarrhoea and constipation.

As the disease progresses, the patient becomes weak, irritable and depressed and the gastro-intestinal discomfort and gaseous distention increase gradually. In advanced cases the complexion assumes a peculiar muddy pallor. The abdomen becomes distended and takes on a doughy feel. The number of soft stools may increase to five or six daily and attacks of colic may be frequent. The history sometimes indicates that the symptoms are promptly aggravated by the consumption of carbohydrate foods. Meanwhile, the tongue becomes red, angry looking, and furrowed; soreness of the mouth increases; there may be burning pain in the oesophagus or in the epigastrium; and ulcers may appear opposite to the molar teeth or under the tongue. In cases of extreme emaciation, active peristalsis of the small intestine may become clearly visible. Dur-

ing remissions, the tongue becomes smooth and pink, soreness of the mouth disappears and all symptoms abate. Rarely, soreness of the tongue may be the only symptom noticed.

The changes in the blood are very variable. In the early stages of the disease and during remissions, the color-index is reduced and the blood changes are of the hypochromic type. When the severity of the symptoms increases, the red cells become macrocytic and hyperchromic. The picture may then be that of Addison's anaemia.

Achlorhydria has been observed in from a quarter to a third of the cases studied. Chemical analysis of the gastric contents is an inadequate index of the presence or absence of the "intrinsic factor" of the gastric secretion (Castle et al: 1935). The intrinsic factor may be present or absent, whether or not hydrochloric acid is present. Signs of combined system disease analogous to those which may appear in Addison's anaemia, are seen occasionally in sprue. In rare instances, they dominate the picture. Tetany may develop in sprue at any stage but especially in association with a downward course of the disease.

The stools may be watery in the early stages of sprue. In other cases they contain much mucus. The typical sprue stool is gray in color, soft, full of minute gas bubbles, sour smelling and abnormally voluminous. Microscopic examination shows great excess of fatty acids, soaps and sometimes of neutral fat as well. The proportionate amounts of these constituents is variable. Muscle fibers may be seen, but starch granules are absent. Bile pigment is present in the stools in the form of leucobilirubin.

The blood pressure is markedly reduced. It tends to decrease as the disease progresses and to rise with improvement. Thayssen (1932) found that the basal metabolism was frequently increased, and sometimes considerably increased, but Suarez's (1938) observations in Puerto Rico were to the contrary. They both found the blood sugar curve abnormally low. Similar changes, but probably tending to be of lesser degree, have been observed in Addison's anaemia. Fairley (1930) and others have noted reduction of serum calcium in some cases of sprue and particularly in those having tetany. He reported phosphorus at the normal level whereas in parathyroid tetany, phosphorus values are increased.

Certain cases of "non-tropical sprue" present the typical symptomatology of sprue, but a large proportion of cases originating in the temperate zone are atypical.

Diagnosis

Diagnosis is simple when the stools are characteristic, anaemia present the tongue denuded and sensitive, and weakness and emaciation pronounced. Diagnosis may be difficult in mild cases, during remissions, and in atypical cases. The stools in Addison's anaemia are neither copious nor gray in color, emaciation is strikingly absent, and the color of the skin is lemon-yellow in contrast to the muddy discoloration seen in well marked cases of sprue. Certain borderline cases, however, might be classified by

competent observers either as sprue or as Addison's anaemia. The spleen in sprue is not enlarged but in Addison's anaemia it is often palpable.

In pellagra, the lesions of the tongue, the weakness, the emaciation, and the diarrhea may suggest sprue but the stools are neither fatty nor voluminous. In pellagra, the anaemia is seldom pronounced. It is still less likely to be of the macrocytic type. There are borderline cases, however, which present some of the characteristics of both diseases. These and other atypical cases are to be regarded as instances of multiple deficiencies. Roentgenological observations by Mackie, Miller and Rhoads (1935) and others, indicate that, in sprue and in multiple deficiency states, the activity of the small intestine becomes curiously irregular.

Gee-Herter disease or coeliac disease, usually seen in young children, the idiopathic steatorrhoea of adults, and atypical cases of non-tropical sprue appear to be closely allied to sprue. Fairley (1936) has stated that "In contra-distinction to coeliac disease and idiopathic steatorrhoea, hypo-calcaemia in tropical sprue never leads to osteomalacia, bony deformity or spontaneous fracture. Furthermore, gross osteoporosis must be relatively rare." He attributes the hypo-calcaemia of steatorrhoea and of sprue to defective absorption of calcium rather than to parathyroid disease and he quotes Linder and Harris (1930) who believed that defective absorption of vitamin D was the major cause of tetany in steatorrhoea. The comparative rarity of bone lesions in cases of tropical sprue has been attributed to the beneficial effects of greater exposure to sunlight.

Fatty diarrhoea may occur in gastrojejuno-colic fistula or in pancreatic disease. Thayssen (1932) says that the fatty diarrhoeas of pancreatic origin are usually associated with increased elimination of nitrogen in the faeces, diabetic glycosuria or alimentary glycosuria, and a blood sugar curve of diabetic type. On the other hand, when there is hyperchromic anaemia, this is indicative of sprue.

The atrophy of the muscles in general, which is extreme in some cases of sprue, occasionally leads to a mistaken diagnosis of progressive muscular atrophy. The atrophy in the latter disease is limited to muscle-groups and the condition tends to be hereditary. The emaciation of sprue sometimes leads to an erroneous diagnosis of cancer or of tuberculosis. Intestinal amoebiasis, chronic bacillary dysentery, hookworm disease, or tuberculosis, may be associated with sprue.

Prognosis.—Mild cases of sprue respond rapidly to adequate treatment with liver extract. Not only does the condition of the blood improve, but the soreness of the mouth and the gastro-intestinal symptoms quickly disappear. Even in severe cases of long standing, the improvement may be dramatic. Unless adequately treated, however, severe cases are ultimately fatal within a period varying from about one to fifteen years.

In cases in which the intrinsic factor has been absent, it may reappear following liver therapy. Unlike cases of Addison's anaemia, which generally require maintenance doses of liver extract to prevent recurrence, sprue may be permanently curable.

Treatment

It is now well known that administration of liver extract not only benefits the macrocytic anaemia of sprue, but that the extract is capable of overcoming the mouth lesions and the gastro-intestinal symptoms as well.

Castle (1935) observed that oral administration of liver extract sufficed, in some cases, to control the lingual and gastro-intestinal symptoms, but that in the majority of cases improvement was not remarkable until after the extract had been administered parenterally. His usual initial dosage of the extract was the amount derived from 50 to 100 grams of liver given once a week or that from 10 grams injected daily. Vomiting or profuse diarrhoea were sometimes relieved within twenty-four hours. Lingual symptoms were relieved and diarrhoea was usually controlled within a week. Epigastric distress and flatulence were correspondingly improved. Within two weeks, as a rule, the stools were formed. Meanwhile, the sense of well-being and the appetite were regained. Weight and strength increased gradually. It was found, however, that larger doses of the extract were needed in some cases and, especially, in those of long standing Dosage must be adequate to induce initial improvement in each particular case. A somewhat smaller maintenance dose, administered once a week, may be required to prevent relapse. The variability of dosage required for individual cases is even more pronounced than in Addison's anaemia and the requirement is apt to be much higher in sprue.

Parenteral rather than oral administration is the usual method of choice. Probably this method is necessary when the "intrinsic factor" is lacking. The intravenous route has advantages when extract from as much as 100 Grams of liver is required daily. Pathologic changes in the gastro-intestinal tract resulting from extreme chronicity of the disease or from complications, render treatment ineffective in a few cases.

Diet.—In some cases of sprue, the anaemia and other symptoms respond to dietary treatment alone, but it is believed that diet can only be effective in improving the blood-picture when the "intrinsic factor" is present. Oral administration of liver extract will sometimes cause a reticulocyte response. More pronounced effects are obtained by parenteral injection. The rise in the erythrocyte count in response to treatment is seldom as rapid as it usually is in Addison's anaemia. As in some cases of Addison's anaemia, so in certain cases of sprue, there is a deficiency of iron. Cure of the anaemia in these cases is attainable only after the administration of iron in addition to liver extract. When hydrochloric acid is lacking it should be administered to the patient by mouth.

Diet has been relegated by the newer methods of treatment to a position of lesser importance. However, a high protein, high vitamin, non-irritating diet containing little carbohydrate or fat may help to relieve symptoms before the specific methods of treatment have produced their effects. More or less dietary restriction can advantageously be continued in some cases. Such restrictions are necessary for some elderly

persons (Suarez: 1938). Persons who have recovered symptomatically from sprue as a result of treatment, should be cautious as to diet and they may require a maintenance dose of liver extract.

Neurologic symptoms like those of combined system disease, when present, may be expected to yield slowly to liver therapy. When there is tetany or osteoporosis, calcium lactate and vitamin D are indicated.

Persons who have contracted sprue in an endemic area and who return thereto, must be closely watched because the chance of recurrence is considerable (Miller and Barker: 1937).

Prevention

Owing to doubt as to the fundamental cause of sprue, rules for prevention cannot be formulated with confidence. It is clear, however, that debilitating influences in general should be guarded against; that digestive disorders, especially dysentery, should be treated promptly and effectively; and that the diet should be well balanced and nutritious. It should not contain an excess of carbohydrates. It is believed also that adequate exercise taken regularly helps to maintain the digestive functions in a normal condition. Harrison, et al., (1943) in pointing out that low levels of calcium in sprue are usual, found serum potassium at very low levels in 2 cases of sprue.

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Addendum

In a review of the recent literature on the subject, one finds that the etiology of sprue in at least some respects has not yet been definitely elucidated. The main points that have been particularly emphasized in the sprue syndrome, are glossitis, steatorrhoea, emaciation, progressive anaemia (usually macrocytic) hypochlorhydria, sometimes achylia with loss of intrinsic factor, hypocalcaemia, a general avitaminosis and sometimes pigmentation of exposed parts. Some observers believe that there exists no fundamental difference between tropical and nontropical sprue. However, the number of cases of non-tropical sprue so far described, does not apparently permit of any generalization to this effect. Other authors have suggested that the sprue syndrome may be evolved from delayed coeliac disease. Rodriguez Molina (1941) from the study of 100 cases in Puerto Rico concurs in the belief that the sprue syndrome is a deficiency state and that the anaemia is caused by gastro-intestinal dysfunction combined with failure of adequate absorption of nutritional substances essential in erythropoiesis and that gastro-intestinal symptomology and changes in the skin and mucosa are associated with a deficiency in vitamins A and B.

Shattuck (personal communication, 1942) remarks that it seems probable that sprue is not exclusively a food deficiency disease inasmuch as it occurs rarely, if at all, in typical form in Africa. It might be regarded as a disease of metabolism of unknown origin in which food deficiency plays a part. Hotz and Deucher (1941) point out that a study of the radiographical changes in the small intestine in *non-tropical* sprue suggests that the main etiological factor lies in the presence of an unascertainable and not easily explicable absorption defect in the intestinal mucosa. However, the pathological changes which have been encountered at many autopsies do not clearly explain the peculiar intestinal dysfunction in sprue. Snell, Mackie, Miller and Weber have reported radiological features, especially narrowing of the ileum, alteration of atonicity and spasticity, a coarsely-striated mucosal relief pattern, and increased motility. Ludin has observed changes in the intestinal wall of the duodenum jejunum and ileum due to chronic infiltration, oedema of the mucosa or atrophy, while Ruhlmann found oedema of the mucosa and stagnation of the meal in the lower ileum in some cases.

Hotz and Deucher from the study of 8 cases of non-tropical sprue, reported that the changes in the small intestine demonstrated by the radiological method are the result of intestinal hurry and interference with the normal mixing of the intestinal contents.

Antogonini (1941) points out that steatorrhoea is no longer regarded as an explanation of dysfunction of the hepatopancreatic apparatus but rather as a disturbance of resorption from the intestinal tract and that this is defined by 3 syndromes. 1. Coeliac diseases—Gee-Herter disease (idiopathic steatorrhoea) and sprue. 2. Hypo- and avitaminosis B_2. 3. Adrenal insufficiency (Addison's disease).

Olleros (1940) has carried on bacteriologic investigations of the gastric mucosa in sprue by gastroscopic methods and found that in 92% of the sprue cases the gastric mucosa was colonized by intestinal flora. He suggests that under tropical conditions the antibacterial defences which normally predominate in the intestinal tract are broken down and that this acts as a predisposing factor in the genesis of sprue. The normal gastric mucosal surface with a pH 1.4–1.6 is sterile; the duodenum at pH 5.2–6.2 contains a few Gram-positive cocci; the upper jejunum at pH 6–7.0 Gram-positive cocci and a few Gram-positive and negative bacilli. The ileum at pH 6.8–8.0 contains a rich bacterial flora of the faecal type. There is, therefore, a distinct relationship between the pH in different regions of the intestinal tract and the prevailing bacterial flora.

Manson-Bahr (1941) has for many years had a wide experience with the disease and in several recent publications has carefully considered the etiology of sprue and the sprue syndrome, and critically reviewed the entire subject. He writes that it may be assumed that tropical sprue represents the fully developed picture of small intestine deficiency and is presumably due to previous damage to the intestinal mucosa. He writes, that the main lesion of sprue is confined to the small intestine, is suggested by the diaphanous appearance postmortem of this viscus in advanced cases, as well as by the abundantly proven clinical observation that abdominal distention is due to

inflated coils of the intestine. He presents the hypothesis that gastro-duodenal inefficiency (and absence of intrinsic factor) is responsible for pernicious anaemia that jejuno-ileal inefficiency is responsible for the sprue syndrome and that ileo-caecal inefficiency is responsible for pellagra. He also points out that neither achylia-gastrica nor hypochlorhydria is present as an invariable rule in sprue and that Castle found the intrinsic factor present in sprue even in cases with complete achlorhydria. Rodriguez Molina (1941) found free hydrochloric acid present in the gastric juice in 82 cases. Leitner (1942) points out that while it appears that gastric acidity has no definite bearing on the progress of the disease, disturbances of gastric secretion are too frequent in sprue to be completely disregarded. He also remarks that it may be permissible to stipulate that there exists an additional unknown factor in gastric secretion and that in addition to gastrin (identical with histamine) a second gastric hormone has been prepared from the acid extract of the pyloric mucosa which exerts no effect on blood pressure, pancreatic or bile secretion, but when absorbed by the small intestine produces a gastric flow rich in acid but poor in pepsin. Another significant fact has been demonstrated by Laurent and Sinclair who have shown that vitamin B_1 may be destroyed in the stomach in achlorhydria.

The normal and natural stimulus for the contraction of the villi and absorption is *villikinine* which is extractable from the intestinal mucosa by hydrochloric acid, so that it can now be stipulated with some confidence that some factor in the gastric juice, usually combined with hydrochloric acid, is jointly responsible, not only for the movements of the villi, but also for the preservation of vitamin B. The permeability of the epithelium of the villi is also an important factor.

Leitner has critically reviewed the literature and the physiology of the small intestine in its application to the etiology of sprue and his article should be consulted by all those especially interested in the subject. In his conclusion he has expressed the following views as an explanation of the chain of events involved in the mechanism of the sprue syndrome.

1. "*Primary Cause.*—Breakdown of normal absorption in the upper part of the small intestine (due to different causes).

2. *Secondary Causes.*—Deficiency in gastric secretion and hydrochloric acid necessary for coordination of intestinal functions.

3. Achlorhydria, which affects motility of the villi and decreases the vitamin B content of food.

4. Stagnation and malabsorption, which produce abdominal discomfort and flatulence.

5. As a consequence of achlorhydria, migration and multiplication of intestinal flora (*Bact. coli*).

6. Consequent breakdown of iron metabolism in relation to bone-marrow and haemoglobin, producing megalocytic anaemia.

7. Haemoglobin metabolism perverted to increasing amounts of porphyrin.

8. Bilirubin excretion reduced; bilirubin serum content increased.

9. Following liver damage bile acids decreased; in turn reducing hydrotropy and fat absorption.

10. Unresolved fatty acids in the small intestine forming insoluble calcium salts; this affects the bones and then the whole electrolyte equilibrium. Development of this stage is slow and may last years.

11. Increasing liver dysfunction; excessive porphyrinuria whereby Meissner's plexus is paralysed; motility of villi is disturbed. Breakdown of cytochrome-enzyme system and steatorrhoea.

12. Owing to already present dysfunctions an acute vitamin B deficiency is thereby produced.

The clinical manifestations resulting from this successive chain of events may eventuate in sprue or possibly in pellagra." Stannus (1942) has written a critical review of sprue, has formulated new ideas in regard to the pathogeny, and made observations for further investigations. His article published while this book is in press, should be studied by all those interested in the subject. He considers the primary failure in sprue is one of phosphorylation, the result of defective enzymic action and that sprue is properly placed among the diseases of malnutrition. (For reference to addendum see p. 1029.) For critical review of the literature—see Stannus: *Trans. Roy. Soc. Trop. Med. & Hyg.* December, 1942.

Chapter XXXII

DEFICIENCY OF VITAMIN A; THE VITAMIN B-COMPLEX

Definition.—Deficiency of vitamin A is manifested especially by lesions or disordered function of the eye and by changes in the skin and in growing teeth. Xerophthalmia, keratomalacia, night blindness, and cornification of epithelial structures are among the characteristic lesions caused by deficiency of vitamin A.

Vitamin A.—The several carotenoid pigments which are included under the name of carotene are yellow or red in color. They are synthesized by plants and, in the animal body, they are convertible into vitamin A. Carotene is also called provitamin. Beta-carotene is used as the basis of the international unit because of its superiority as a source of vitamin A. It is stored in the body both as provitamin and as vitamin A.

Incidence.—Recognizable signs of vitamin A deficiency are by no means uncommon in infants and in young children. In adults, well marked cases seem to be infrequent, except that regional outbreaks have occurred when groups of people have been subjected to such dietary privations as may occur in time of famine or in war. Sailors, prisoners, and laborers in India and elsewhere have been afflicted, as have individuals when subjected to dietary restrictions. Infectious diseases, gastro-intestinal diseases, disorders of fat absorption, diarrhoea, or advanced disease of the liver may interfere with absorption of vitamin A and may thus cause signs of deficiency to appear.

The true incidence of vitamin A deficiency is not known. Probably the lesser degrees of deficiency are common and widespread in the Tropics and elsewhere. Vitamin A deficiency should be looked for wherever malnutrition exists. As a rule, it is associated with other kinds of nutritional defects.

ETIOLOGY

Vitamin A deficiency is caused by deficient ingestion of food containing vitamin A or the carotenoid pigments from which vitamin A is derived, or from failure of the body to absorb and to utilize these substances. Normal bile, being concerned with the absorption of fats, probably aids the absorption of vitamin A from the intestine. Advanced liver disease may interfere with storage of this vitamin. Rapid growth, pregnancy, fever and other conditions which increase metabolism, enhance the requirement for vitamin A. The carotenemia which has been observed in the blood of diabetics by Brazer and Curtis (1940) may be due to inability of the body in these cases to convert carotene into vitamin A.

Liquid petrolatum, ingested in therapeutic dosage, absorbs carotene from the food-content of the intestine (Curtis and Ballmer: 1939) unless it has been previously saturated *at body temperature* with carotene. The same may be true of other fats and oils which normally contain little or no carotene. The etiological implications of these facts seem to be significant.

Physiology.—Vitamin A is necessary for vision, for the maintenance in normal condition of various epithelial structures, including the teeth, for storage of fat, and for growth.

In the eye, vitamin A is needed not only for the formation of visual purple, but also to prevent degeneration of the cornea and other parts of the eye. Deficiency of vitamin A causes defective or delayed formation of visual purple.

The human body has considerable power to store vitamin A. The liver is the principal reservoir. At birth, the liver contains little of this vitamin but it tends to accumulate with advancing years. Cow's colostrum has an extremely high vitamin A activity and human colostrum is about three times as active as is human milk. Thus, the infant is normally provided with large amounts of vitamin A at the time when little of it is present in the liver. Absorption from the intestine is variable and by no means complete. Apparently, vitamin A is not normally excreted in the urine but it is present in the circulating blood.

PATHOLOGY

The pathology of vitamin A deficiency has been described in detail by Bessey and Wolbach (1938). Effects of deficiency of vitamin A are manifested in many epithelial structures. The characteristic changes are atrophy of epithelium, proliferation of basal cells, and consequent formation of stratified, keratinized epithelium. The changes are identical wherever they occur.

In man, the lesions of epithelial structures are found in various parts of the eye, in the enamel-forming organ of the teeth, the nose and accessory sinuses, the trachea and bronchi, the renal pelves, the bladder, the prostate gland, the uterus, the testes, the sweat and sebaceous glands, the hair follicles and the skin. The pancreas, the lacrimal glands, and perhaps the salivary and parotid glands may be involved. Analogy suggests that lesions of the gastro-intestinal mucosa might result from deficiency of vitamin A.

Loss of body fat, retardation of growth, haemosiderosis of the liver and spleen, and atrophy of the bone marrow associated with anaemia, lymphoid hypoplasia of the spleen and degeneration of skeletal muscles may be found in vitamin A deficiency but they are not specific lesions. The lesions of vitamin A deficiency are usually associated with signs of deficiency of other food factors.

Wolbach* does not believe that there is any clinical evidence of the production of neurological lesions in man as a result of deficiency of

* *Personal communication: October* 1940.

vitamin A. On the basis of work done in his laboratory, he has reached the conclusion that it is impossible, by a diet deficient in vitamin A, to produce neurological lesions in animals approaching adult size. Wolbach and Bessey (1940) have reported that in growing rats during the first few weeks of life, deficiency of vitamin A can stop the growth of bone. Lesions of the nerve roots then follow as a result of overgrowth of the central nervous system.

SYMPTOMATOLOGY

Eyes.—Hemeralopia is an early sign of deficiency of vitamin A. This disorder is manifested by defective vision in subdued light, or by delayed adaptation to subdued light, or after exposure of the eyes to bright light. The symptom indicates delayed or defective formation of visual purple. Conjunctivitis, itching and burning of the eyelids and photophobia indicates a later stage of the disorder. Some authors, perhaps erroneously, have attributed like symptoms to riboflavin deficiency (p. 1036). Still more advanced cases show dryness and reduced sensitivity of the cornea and of the conjunctiva (xerophthalmia). The cornea may show light brown pigmentation, the lids may twitch, and the patient may see dancing specks or glittering images. Finally, Bitot's spots, which resemble flecks of dried foam, may appear on the cornea; or softening and ulceration may occur (keratomalacia). Permanent damage to the eyes and even blindness may result. Lesions are bilateral as a rule.

Teeth.—Damage to the enamel-forming organ disturbs the formation of dentine so that growing teeth become soft or develop abnormally.

The skin is abnormally dry and rough. The roughness is produced by cornification which occurs especially around the hair follicles on the extensor and outer surfaces of the arms and legs. This feature is far more common in adults than in infants. There may be generalized pigmentation of the skin. Acneform eruptions are common. Changes in the hair and in the nails have been reported.

Other signs and lesions which have been attributed directly or indirectly to deficiency of vitamin A, include dryness of the mouth, sinusitis, dry cough, bronchiectasis, bronchial obstruction and atelectasis, deficiency of gastric hydrochloric acid, digestive discomfort, diarrhoea, pyelonephritis, cystitis, prostatitis, abortion, testicular atrophy, nervousness and neurologic lesions involving the legs and causing more or less disability. The growth of children is stunted. A deficiency of vitamin A has been suggested as a factor in the production of lathyrism (p. 1203).

It is doubtful whether neurologic lesions in man are ascribable to deficiency of vitamin A alone. If so, they are most likely to be found in infants and children when growing rapidly (p. 1030). Probably there is a relationship, in some cases, between stone formation in the genito-urinary tract and vitamin A deficiency. Observations made in Java support this view.

Pneumonia is a common cause of death in infants who have vitamin A deficiency. Various other infectious processes are frequently associated

with deficiency of vitamin A. It appears that this deficiency may become a contributory cause of infection by damaging epithelial structures.

DIAGNOSIS

The presence of hemeralopia or of the more characteristic lesions of the eye, should lead to the suspicion of vitamin A deficiency. Hemeralopia can occur, however, in connection with various other diseases of the eye. It cannot be detected in infants and in young children. A useful sign of vitamin A deficiency in them can be elicited by retracting the lids for five minutes. If the cornea then becomes dry and granular in appearance, this is a sign of vitamin A deficiency. Keratinized epithelial cells may be demonstrable by wiping a spatula gently across the cornea and then staining the cells so scraped off. Keratinized epithelial cells may also be found in scrapings from then ose, the mouth, or the vagina, or in the urine.

Photometric examinations of eyes have been extensively used for recognition of the earlier stages of hemeralopia. Because the margin of variation in normal individuals is large, such examinations seem to have a limited value for diagnosis. This test and other features of vitamin A deficiency have been discussed in detail by Jeghers (1937).

Hemeralopia is usually the earliest recognizable sign of vitamin A deficiency. The visible lesions of the eye appear at a later stage. Dryness and roughness of the skin with or without itching, is suggestive, but papular cornification of the skin about the hair follicles has been described as characteristic by several observers. It is said to occur especially on the extensor surfaces of the extremities or over the shoulders. To differentiate between these follicular lesions and those commonly seen in scurvy might be difficult were it not for the fact that they are usually associated in scurvy with petechial hemorrhages. Lehman and Rapaport (1940) studied the cutaneous manifestations of vitamin A deficiency in children. Their investigations indicated that so-called keratosis pilaris, lichen pilaris, lichen spinulosus, icthyosis follicularis and other synonyms, are merely descriptive terms for manifestations of vitamin A deficiency.

Information should be obtained about the diet of the patient, with special reference to foods containing vitamin A. It should be known whether the patient has or has had any disease which interferes with absorption of food. In this connection, diseases of the liver or the pancreas, sprue, and persistent diarrhoea or vomiting are especially important. Chronic wasting diseases and cases of acute illness, such as typhus or typhoid fever, when severe, restrict the ingestion and absorption of food and can lead to keratomalacia which is dependent, probably, on deficiency of vitamin A.

Methods for estimating the carotene and vitamin A content of the blood plasma seem to be of little value for diagnosis.

TREATMENT

Diet.—Because vitamin A deficiency is generally associated with signs of deficiency of other food factors, treatment should include a balanced

diet, rich in all known food factors. Resistance to infection is believed to be increased by administration of vitamin A, only when the supply of vitamin A in the body is inadequate.

Sources.—The richest sources of vitamin A are the cod and especially the halibut liver oils. Carotene is abundant in most of the green, leafy vegetables and in some of the yellow or red vegetables and fruits. There is a good deal of it in milk, butter, cheese, egg-yolk, and fresh yeast. In addition to their varying content of carotene, milk and butter contain vitamin A, which is colorless. Therefore, the color of milk is not an index of its value as a source of vitamin A. Butter usually contains artificial coloring matter.

Carotenoids and vitamin A are soluble in fats and oils. The activity of vitamin A or of carotene is rapidly destroyed at high temperatures by an oxidizing agent. This point is well known to manufacturers of canned foods. Many such foods, as marketed today, are believed to be valuable sources of vitamins. Dried or dehydrated foods are relatively deficient in vitamin A. Red palm oil, an important article of diet in parts of Africa is rich in carotene.

Dosage.—The minimum daily requirements for vitamin A are not accurately known. Booher (1938) believes that 6000 to 8000 units of vitamin A (U.S.P. or International Units) should be provided for the growing child. She recommends 5000 units or more for pregnant and nursing women. Visual acuity in adults has been restored in two or three weeks by daily administration of the carotene equivalent of 10,000 units of vitamin A (Jeghers: 1937). Concentrated solutions of carotene in oil are now available for therapeutic use (New and Nonofficial Remedies: 1939). The optimum dosage of carotene and of vitamin A is uncertain. Spies (1939) has used up to 50,000 units in the form of concentrates. Visual disturbances may respond rapidly to treatment but the skin lesions may persist for 4 to 14 weeks (Youmans and Corlette: 1938).

Absorption of fat seems to aid in assimilation of carotene. Conversely, a diet too low in fat or deficiency of bile in the intestine may reduce absorption of carotene. Steatorrhea from any cause, biliary obstruction, and the taking of liquid petrolatum may interfere with the absorption of carotene and of vitamin A. It is probable that the utilization of carotene and of vitamin A may be disturbed in severe cases of liver disease. When the normal flow of bile into the intestine is reduced, bile should be administered to the patient. When factors are present which may operate against absorption of carotene, larger dosage of carotene or of vitamin A is indicated.

Toxicity.—Evidence is lacking that vitamin A, *per se*, is toxic to man or animals, but experiments on animals indicate that cod liver oil, given in considerable dosage, is toxic for certain kinds of animals and perhaps for man. Muscular dystrophies and degeneration of the heart muscle have been attributed to constituents of the oil. Until more is known about this matter, some caution in the use of large and repeated doses of highly concentrated preparations of liver oil would seem to be advisable.

Yeast and "natural foods" are believed to have some protective action against the toxic substances of fish liver oil. Clausen (1938) has discussed the question of toxicity of vitamin A preparations.

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The Vitamin B-Complex

Dr. Otto A. Bessey has kindly prepared the following statement about the Vitamin B-Complex.

The term "vitamin B-complex" refers to a group of water-soluble dietary factors (vitamins) which have become grouped under one term as a consequence of historical development and because of their similarities in properties and occurrence together in yeast and liver.

Confusion in terminology has developed due to the rapid progress in investigative work in this field and the subsequent unexpected multiplicity of factors. Different terms have been applied to newly discovered factors and specific terms became entrenched in the literature before the existence of separate entities was established. The terminology which appears in publications dealing with these factors and its meaning will vary, depending on the country from which it came and the time at which it was written.

Soon after attempts had been made to determine the nature of all dietary essentials necessary for the rat, McCollum (1916) proposed the name "water-soluble B" for a newly discovered factor and presented evidence that it was similar to the antiberiberi factor that Eijkmann (1897) had previously shown would prevent experimental polyneuritis in birds. In 1920, Drummond suggested that the term vitamin (previously coined

by Funke), with qualifying letters, should be used to designate the members of this rapidly growing list of dietary essential factors until such time as the factors could be isolated and identified as pure chemical compounds. It was soon found that the factor which had been designated as "vitamin B" was multiple in nature, a heat-labile fraction contained the antineuritic factor, while both this and a heat-stabile factor were necessary for growth in the rat. At about the same time (1925), Goldberger and Tanner showed that pellagra was due to a dietary deficiency and could be prevented by a heat-stabile factor present in the yeast. This factor had properties similar to the heat-stabile rat growth factor. They proposed the name pellagra preventive factor (P. P. Factor) for this dietary essential. This term was generally used until 1937, after which time it was gradually replaced by "nicotinic acid" which had been identified as the principle chemical entity in question. It had been found that "nicotinic acid" also prevents black tongue in dogs thus establishing the correctness of the early assumption that this disease in the dog corresponds to pellagra in man.

In 1927, the British Accessory Food Factors Committee proposed a system of nomenclature in which the term "vitamin B" was to be used for the developing complex, vitamin B-1 for the antineuritic factor, and vitamin B-2 for the more heat-stabile part of the complex. As evidence for other factors appeared, they were designated as vitamin B-3, vitamin B-4, vitamin B-5, etc.

A committee on Vitamin Nomenclature of the American Society of Biological Chemists recommended, in 1929, that the term "vitamin B" be used to designate the antineuritic factor and "vitamin G" be used to designate the heat-stabile fraction of the complex. The use of the term "vitamin G" has been confined almost exclusively to the American literature. The terms "vitamin G" or "vitamin B-2" have been used in some instances in reference to the pellagra preventive factor.

Kuhn (1933) demonstrated that lactoflavin, a yellow, heat-stabile pigment present in many natural products including yeast and liver, was necessary for growth in the rat. Additional evidence showed that it was this factor which had been measured by rat growth methods as "vitamin G" in America and vitamin B-2 in Great Britain. Vitamin B-2 has subsequently been used extensively in the German and in the British literature as a designation for this factor. In America, the term "vitamin G" has been used. In 1937 the American Committee on Nomenclature recommended that this factor be designated as riboflavin and that the term vitamin G or vitamin B-2 be no longer used. This committee also suggested that the antineuritic factor be known as thiamin or vitamin B-1 and that the term vitamin B without a subscript be no longer used. Many European publications have used the term aneurin in reference to the antineuritic factor.

Thiamin (heat-labile), riboflavin and nicotinic acid (heat-stabile) are pure chemical entities of established importance in human nutrition. Evidence for the existence of a number of additional *heat-stabile* members

of the B-complex has come from separation procedures on liver and yeast, and from the response of rats, pigeons, chicks and dogs to these fractions and to treatment with various types of experimental diets. Undoubtedly, many of these factors will be shown in the near future to be important in human nutrition.

Vitamin B-3, and vitamin B-5 are designations of supposed growth factors for the pigeon.

Vitamin B-4 a heat-labile factor supposedly associated with specific paralytic symptoms in the rat and chick.

Vitamin B-6 (factor Y, adermin) a pure compound which prevents a dermatitis in rats and an anaemia in dogs.

Pantothenic acid (filtrate factor) a pure compound which prevents a dermatitis in chicks and is a growth requirement for the rat.

Gray hair factor, denotes a fraction which prevents the development of gray hair in rats, foxes, and other animals kept on certain experimental diets.

Factor W, designates a supposedly necessary growth factor for the rat.

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Chapter XXXIII

BERIBERI

Synonyms.—Polyneuritis Endemica; Barbiers; Kakké (China and Japan); Maladie des Sucreries (French Antilles); Hinchazon (Cuba); Inchaçao or Perneiras (Brazil); Maladie des Jambes (Louisiana); Alcoholic Neuritis.

Definition.—Beriberi is a disease of nutrition which is attributed to inadequate ingestion, absorption, or utilization of the heat labile portion of the vitamin B complex which is usually designated as vitamin B-1 or as thiamin. Typical cases are characterized by neurological lesions, involving particularly the peripheral nerves of the limbs, or by acute congestive failure of the heart which develops in the absence of lesions of the valves, hypertension, coronary disease, or of pronounced changes in the myocardium.

History.—Beriberi has long been known in parts of the tropics and subtropics. Its occurrence, in modified form, among fishermen and sailors on the high seas was recognized a generation ago. The discovery of beriberi in Newfoundland in 1914 has proved that this disease could develop in a cold climate. Evidence which has accumulated during the past ten years indicates that "alcoholic neuritis" is to be regarded as beriberi in the alcoholic subject; and that beriberi may be "conditioned" by a considerable number of other diseases or circumstances in which nutrition is disturbed.

Geographical Distribution.—Beriberi has been particularly prevalent in southern China, Japan, Malaya, the Dutch East Indies and the Philippine Islands. Notable outbreaks have occurred in Brazil, in other tropical parts of South America, and in Africa. Many cases occurred in a garrison in Puerto Rico in 1918. In 1928, numerous cases of beriberi were recognized among rice farmers of Louisiana. The incidence and distribution of sporadic cases in the temperate zones is imperfectly known.

A good many years ago, beriberi virtually disappeared spontaneously from the Amazon Basin. More recently, the application of effective methods of prevention has greatly reduced its prevalence in the Far East.

Incidence.—Race, age and sex have little if any influence, *per se*, on susceptibility to beriberi. Outbreaks of the disease have been associated at times with insanitary conditions in garrisons, prisons, asylums and on ship-board. An epidemic of infectious diarrhoea, or of some other infectious disease, may condition an outbreak of beriberi. In South China, and in some other localities, beriberi prevails particularly under seasonal climatic conditions which are characterized by heat and humidity. It

would be rash to assert that climatic conditions have no direct influence, but it is more probable that coincident modifications of diet are of greater importance.

An ill-balanced diet in which "polished" rice or other starchy food predominates is responsible for most of the cases of beriberi. In Newfoundland, particularly during the winter months, white flour plays a rôle like that of polished rice.

Etiology

Vitamin B-1.—It is generally believed that the more characteristic symptoms of beriberi are caused by deficiency of vitamin B-1. Such deficiency may be brought about by inadequate ingestion, by defective absorption and, probably, by metabolic disorders which interfere with utilization of the vitamin after absorption from the intestine.

The requirements of the body for vitamin B-1 increase with the metabolic rate and with the caloric value of ingested food. Among conditions which increase the need for vitamin B-1 are arduous work, febrile diseases, hyperthyroidism, pregnancy and lactation. Absorption may be seriously impaired by continuing diarrhoea, by lesions of the gastro-intestinal tract, or by short-circuiting operations which involve the intestinal tract. Advanced disease of the liver, probably, restricts the storage and utilization of vitamin B-1

Ineadequat ingestion of vitamin B-1 may occur in connection with a great variety of conditions which may lead the patient to subsist on an ill-balanced diet. These conditions include certain racial habits, poverty, chronic alcoholism, vomiting of pregnancy, cancer of the gastro-intestinal tract, tuberculosis, persistent anorexia, dietary fadism, and unwise therapeutic restriction of diet. Beriberi in nursing infants is caused by deficiency of vitamin B-1 in the breast milk and this in turn is due to deficiency of vitamin in the diet of the mother or the wet-nurse.

Not all the symptoms which occur more or less frequently in beriberi can be attributed to deficiency of vitamin B-1. In atypical cases, some of the symptoms are caused by deficiency of other components of the vitamin B-complex or by deficiency of other important food factors. Protein deficiency, for example, may be a factor in the causation of oedema. There are numerous cases of combined deficiency in which signs of deficiency of vitamin B-1 may be either dominant or inapparent.

While granting that the polyneuritis associated with alcoholism, pregnancy and gastro-intestinal disturbances is due to nutritional deficiency, and that it is in every way similar to Oriental beriberi, Meiklejohn (1940) believes that the exact nature of the deficiency causing "nutritional neuritis" remains obscure. He said that "it has not been demonstrated that this polyneuritis is due to deficiency of thiamin." Vedder postulated that dry beriberi is caused by deficiency of "X" and that wet beriberi is caused by deficiency of "Y." In his most recently published paper (Vedder: 1940) has said that a diet exclusively of polished rice is as deficient in the vitamin B-2 complex as in vitamin B-1, and that the nerve

degeneration of beriberi may be due chiefly to deficiencies of vitamin A and of the B-2 complex.

There are still a few persons who cling to the idea that beriberi is caused primarily by an infection. The experimental investigations of Fraser and Stanton (1911) in Malaya and of Strong and Crowell (1913) in the Philippines demonstrated very conclusively the deficiency nature of the disease in man. In the latter investigations, in which beriberi was produced by feeding deficient diets to individuals carefully isolated throughout the experiments, not only was its nature shown but also it was conclusively demonstrated that the disease was not an infectious one. The persistence of the view that it is infectious can be explained on the following basis. It is known that large numbers of people, particularly in the tropics, subsist on diets which are barely adequate under ordinary circumstances to prevent the development of beriberi. When in such a group, an outbreak of infectious disease occurs, the requirement for vitamin B-1 is thereby increased. If the infection causes diarrhoea, absorption of the vitamin is reduced. As a consequence of either of these factors, an "epidemic" of beriberi may appear.

The theory that beriberi is caused by a toxic substance which develops in damaged rice, seems to require no more than passing mention. However, rice which has been stored for a long time may deteriorate. The growth of fungi in such rice reduces its vitamin content.

Physiology of Vitamin B-1

Cowgill (1939) has evaluated the recent studies on the physiology of vitamin B-1. Williams and Spies (1938) have dealt with the subject in greater detail.

Storage.—The capacity of the body to store vitamin B-1 is relatively limited. In experimental animals, signs of deficiency may be produced within a period varying from ten days to three or four weeks. Clinical experience indicates that symptoms may appear in man after a few weeks of inadequate diet. Doubtless this period is lengthened when the degree of deprivation is relatively slight. Complete deprivation of vitamin B-1 can scarcely be expected to occur except under experimental conditions. Vitamin B-1 is stored in the liver and in the kidneys. It is nearly as abundant in the normal heart. Even in fatal cases of manifest deficiency of vitamin B-1, some of the vitamin can still be demonstrated in these organs.

Vitamin B-1 is readily absorbed from both the small and the large intestine. Diarrhoea reduces markedly the absorption of vitamin B-1. It seems probable that the vitamin B-1 which has been demonstrated in the faeces is synthesized there by certain bacteria.

Excretion.—Vitamin B-1 is excreted in the urine and in human milk in amounts which vary with the diet (Cowgill: 1939). Harris and Leong (1936) believed that a daily excretion of less than 12 I.U. of vitamin B-1 in the urine is presumptive evidence that the diet is deficient in this vitamin.

Functions of Vitamin B-1.—Disorders of gastric secretion, peptic ulcer, alterations of motility and tonus of the gastro-intestinal tract, and certain cases of chronic colitis have been attributed to deficiencies of parts of the vitamin B-complex. It does not seem possible as yet to decide whether deficiency of vitamin B-1 alone can cause any of these conditions. Anorexia and other mild digestive disorders are frequently attributed to deficiency of vitamin B-1.

The normal heart is not influenced by administration of pure vitamin B-1. Therefore, no beneficial effect is to be expected from the use of this

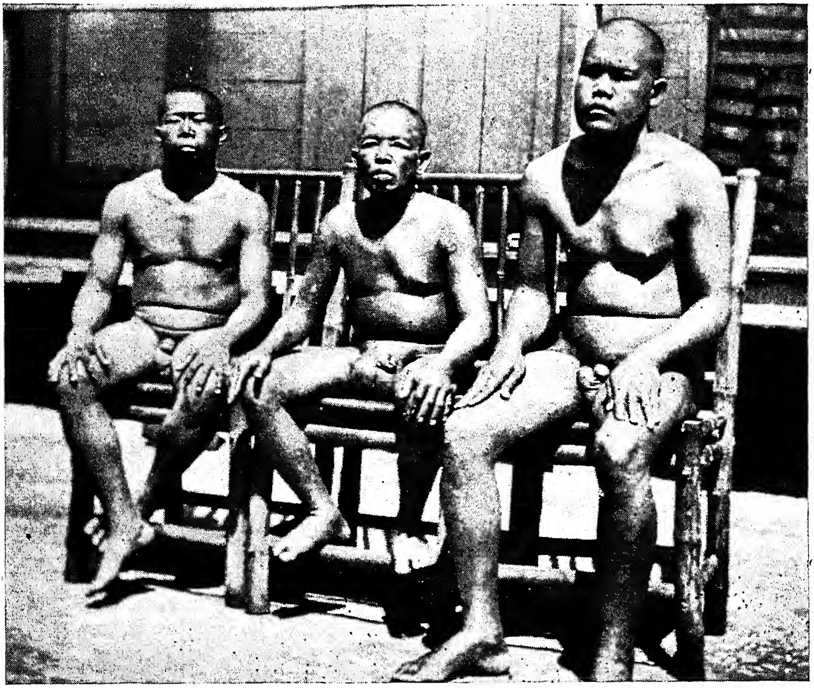

FIG. 226.—Wet form of beriberi.

vitamin except in the presence of deficiency of this substance. The disorders of the circulation referable to vitamin B-1 deficiency are discussed under Wet Beriberi (p. 1045).

Widespread degenerative changes which may occur in the nervous system have been attributed to deficiency of vitamin B-1. The lesions are not specific in character. A number of clinical varieties of neurological degeneration, which were formerly ascribed primarily to some toxic or infectious agent, are believed now to be caused essentially by deficiency of vitamin B-1. These conditions are discussed under Dry Beriberi (p. 1044).

Investigators agree that vitamin B-1 plays an important rôle in the intermediate carbohydrate metabolism. Any condition which increases

the metabolic rate requires an increased amount of vitamin B-1. A diet high in starches, sugar, or alcohol, enhances the requirement. Fats seem to have a sparing action for vitamin B-1. The nature of the relationship of vitamin B-1 to the metabolism of fat, however, is still undetermined. Peters (1936) and his associates believed that vitamin B-1 functions as a co-enzyme in the metabolism of carbohydrates and that it plays a part in the oxidative break-down of pyruvic acid. Accumulation of pyruvic acid or pyruvates in the blood and in the cerebrospinal fluid and excess of them in the urine seem to be related to deficiency of vitamin B-1. This vitamin is essential for normal growth and for maintenance of body weight. Libido is often decreased and the chances of pregnancy are reduced by deficiency of vitamin B-1. It seems highly probable that the functions of various glands of internal secretion are disturbed by lack of vitamin B-1.

Pathology

Heart.—Vedder (1938) has said that deaths from beriberi are due to cardiac hypertrophy followed by sudden dilatation and cardiac failure rather than to lesions of the nervous system, however extensive. The dilatation usually involves chiefly the right ventricle and the right auricle. The left ventricle may be dilated or contracted. The size and weight of the heart is considerably increased. Microscopic examination of the heart muscle has revealed fragmentation, fatty degeneration, and "hydropic degeneration" of muscle fibers. Vedder attributed the fragmentation to post mortem changes. In Java, Wenckebach found hydropic degeneration without evidence of true hypertrophy of the muscle fibers. He believed that the lesions which he observed were characteristic for beriberi. Weiss and Wilkins (1936) observed similar lesions in cases of vitamin deficiency in Boston, but they found lesions of the same character in some of their control cases. The cardiac pathology thus far described seems inadequate to account for deaths of cardiac origin.

Pathology secondary to cardiac insufficiency includes pulmonary oedema, passive congestion of the liver, spleen, kidneys and intestine, accumulation of fluid in serous cavities, and dependent oedema. The oedema may be generalized but it seldom involves the face. Punctate hemorrhages are not uncommonly found under the pleura, in the stomach, and in the duodenum.

Nervous System.—The lesions in the nervous system in beriberi show the characteristics of a degenerative process. Signs of inflammation are absent. Whereas the term neuritis implies inflammation, the term neuropathy, proposed by Wechsler, is more applicable to the neurological lesions of beriberi. Neuropathy may be demonstrable in any of the peripheral nerves, in the cord and spinal ganglia, in the nuclei of the medulla and the pons, in any of the cranial nerves, or in the sympathetic system. Among the peripheral nerves, the sciatic is apt to be involved early and to show relatively advanced lesions. The cranial nerves most frequently involved are the vagi and the phrenics.

The membranes of the spinal cord and brain may show congestion. Degenerative lesions are seldom demonstrable in the cord except by microscopic examination. The anterior and the posterior nerve roots and the motor and sensory tracts of the cord may be involved. Changes in the cord are apt to be more pronounced in the posterior columns and in the nerve roots than elsewhere. Vedder (1938) emphasized the important fact that the splanchnic nerves, the renal plexuses and the branches of the cardiac and of the solar plexuses may show degenerative changes.

Lesions of the axons may lead to, or be concomitant with lesions in the cells from which they spring. The degree of the degenerative lesions

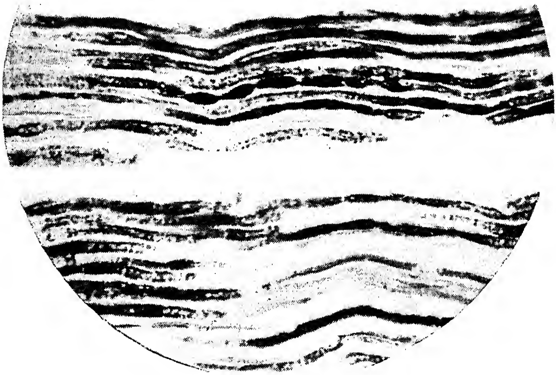

FIG. 227.—Human beriberi. Sciatic nerve, showing degeneration of myelin sheath and in places collections in globules with some fragmentation of nerve fibres themselves. (Strong and Crowell.)

depends largely on the duration of the disease. The microscopic lesions of the axis cylinders consist of destruction of the sheathes with or without fragmentation of the fibers. The nerve cells may show signs of atrophy. In cases of short duration, lesions of the nervous system may not be demonstrable even by histological examination. Usually, the degenerative changes in a nerve are limited to some of its fibers, but an entire nerve may be destroyed. In chronic cases, some of the nerve cells may die. Dead nerve cells cannot be regenerated, so that irreparable disability results.

The muscles supplied by the damaged nerves show more or less atrophy. Neither the atrophic changes in the muscles nor the degenerative lesions of the nerves in beriberi show any characteristic features which are peculiar to that disease.

Symptomatology

The onset of beriberi may be fulminating, rapid or gradual. Non-fatal cases may become chronic. Relapses and recurrences are common. Among the premonitory signs and early symptoms of beriberi are marked general weakness, loss of appetite, and vague symptoms suggesting neurasthenia. Usually, the temperature and the white count are normal. The urine is negative. By the time neurological symptoms appear, the tendon reflexes of the affected limbs are reduced. These reflexes may be lost at a later stage. Tachycardia and enlargement of the heart usually appear

Fig. 228.—Vitamin B (thiamin) deficiency. Sciatic nerve of pigeon. Advanced degeneration of nerve fibres. (Preparation of Dr. R. L. Swank. Courtesy Jl. Exper. Med.)

early. Slight anaemia, due probably to iron deficiency, is not uncommon. In typical cases, the spinal fluid is negative throughout the disease. Serum proteins are sometimes diminished. Probably this change should be ascribed to coincident protein deficiency. For convenience of description, several forms of the disease are recognized: dry beriberi, wet beriberi, atypical beriberi and infantile beriberi. Cases of intermediate or mixed forms are common.

Dry beriberi is characterized by more or less definite signs of neuropathy. The onset, as a rule, is insidious. Weakness of the leg muscles is so often an early symptom that the squatting test has been recommended for diagnosis. In more advanced cases, toe-drop causes the steppage gait and, finally, walking may become impossible. Weakness and atrophy of the muscles develop coincidentally. Sensory disturbances are usually

associated with the motor symptoms, but the disorders of sensation are seldom as prominent as are the motor symptoms. Among the common sensory symptoms are formication and hyperesthesia or blunting of sensation. When the disease progresses, the arms usually become involved in like manner. In well marked and typical cases, the picture is that of flaccid, atrophic paralysis with or without cardiac enlargement and persistent tachycardia. Gradual recovery of injured nerve cells and slow regeneration of damaged neurons occurs in most cases. When improvement has been delayed until after the death of some of the nerve cells, complete recovery is no longer possible.

Wet Beriberi.—Fulminating cases are not rare. They give the picture of congestive heart failure. Usually the onset of cardiac symptoms is

FIG. 229.—Atrophic form of beriberi. Characteristic position of arm and hand. (After Werner.)

rapid. The patient may first notice increasing weakness and a sense of fullness or of pain in the epigastrium. Tachycardia and cardiac enlargement are present. Even slight exertion may produce dyspnoea. At about this time, oedema of the feet and ankles appears. As symptoms increase, the epigastric pain tends to become severe; dyspnoea is followed by orthopnoea with cardiac dilatation and pulmonary congestion; the liver becomes enlarged and sensitive to pressure. Oedema increases markedly. It may become extreme, but it seldom involves the face. Serous effusions are common, but they are difficult to recognize in the presence of marked cardiac dilatation and extensive oedema. Systolic blood pressure falls. The urine becomes scanty, but contains little albumen. Sudden vasomotor collapse may occur. More or less definite signs of neuropathy can usuall ybe elicited by careful examination. Pronounced muscular wasting may be masked by oedema.

In cases which recover, the oedema disappears more or less rapidly. The excess of fluid is eliminated by diuresis. The picture may then become that of dry beriberi.

The mechanism of the circulatory disorders of beriberi is still uncertain. For many years, the cardiac disturbances were ascribed to lesions of the vagi because demonstrable cardiac pathology appeared insufficient to account for them. But Wenckebach (1934) believed that dysfunction of the vagi could not explain the cardiac symptoms. He ascribed them to oedema of the heart muscle with resulting loss of contractility. Weiss and Wilkins (1936) found similar changes not only in circulatory disorders which they attributed to deficiency of vitamin B-1, but also in control cases in which they believed that no such deficiency existed. Their data indicate that not only the heart but also the peripheral circulation may be at fault. It has occurred to me that lesions of the sympathetic nerves may, perhaps, play a part in the causation of the peripheral vascular phenomena.

The conclusions reached by Weiss and Wilkins (1937) in a subsequent paper are so illuminating that they are quoted in full:

"1. Dysfunction of the cardiovascular system resulting from unbalanced food intake is a disease of regular occurrence in the United States. This report is based on a study of 120 such cases, 35 of which were investigated within two years.

"2. The cardiovascular manifestations depend on changes in the nervous system, in the vascular system and in the myocardium.

"3. Tachycardia followed by bradycardia, gallop rhythm, vagal reflex irritability, dilatation of the heart, dyspnoea, orthopnoea and pulmonary congestion, associated with bounding arterial pulsation, arterial 'pistol' sounds, engorged veins, warm skin and oedema are the usual clinical features of severe cases.

"4. The haemodynamics are characterized by low vital capacity of the lungs, high venous pressure and normal arterial pressure, and by a relatively or absolutely increased velocity of blood flow and decreased peripheral utilization of arterial oxygen. The osmotic pressure of the blood is usually moderately low and frequently remains essentially unchanged while the oedema disappears.

"5. The electrocardiograms were normal in but 7 per cent of 67 cases. The main abnormalities consisted in changes in the T-waves and prolongation of the electrical systole (Q-T). The electrocardiographic changes in patients with pellagra or beriberi probably are due to the B-1 component of the vitamin deficiency.

"6. The myocardium often showed 'hydropic' degeneration of the muscle and conductive fibers and increase in the intercellular substances, but unaltered water content.

"7. The cardiovascular disturbances caused by nutritional deficiencies do not form a rigid clinical syndrome. Right ventricular failure, left ventricular failure, arteriolar dilatation and increased blood flow, peripheral circulatory collapse and shock, singly or in combination, have been observed.

"8. The onset of the disease may be sudden or gradual. Patients with the severe form of the disease show a tendency to fever, to bronchopneumonia and to acute fatal circulatory collapse. Under therapeutic measures such as rest, cardiac drugs, diets rich in vitamin B-1 or crystalline vitamin B-1, all the cardiovascular disturbances usually revert to normal.

"9. The clinical symptoms and signs, the blood chemistry, the myocardial changes, the haemodynamics and therapeutic responses correspond to those described in 'beriberi heart' in the Orient. The disease as observed in Boston, however, is characterized by more varied and more generalized involvement of the cardiovascular system.

"10. Evidence is presented indicating that vitamin B-1 deficiency plays a primary rôle in the precipitation of the disease. Alcohol also is a significant factor, not only because it supplies calories without vitamin B-1, but also because its metabolic effect is similar to that of a pure carbohydrate.

"11. The rate of response to vitamin B-1 in 'alcoholic' and 'nonalcoholic' beriberi varies. The arteriolar system shows a more rapid change than the heart. The cardiovascular disorder usually disappears before the polyneuritis. The factors influencing therapeutic responses are discussed.

"12. In normal subjects, as well as in patients with diseases other than vitamin B-1 deficiency, even large doses of crystalline B-1 produce no appreciable effects.

"13. The condition here described bears pertinently on the clinical behavior and the mortality rates of alcoholic and nonalcoholic patients with vitamin 'B' deficiencies (beriberi and pellagra). It may explain the poor reaction of these patients to increases in metabolic rate, such as occur in febrile infections, in hyperthyroidism, or under surgical operations. The therapeutic indications under these conditions are discussed."

Atypical Beriberi.—Doubtless, rudimentary forms of beriberi in which the symptoms are difficult to recognize, are extremely common. Patches of oedema, which have been attributed to vasomotor disturbances, are seen occasionally in beriberi. Lesions of cranial nerves, other than the vagi and the phrenics, occur rarely. Lesions of the phrenic nerves may cause paresis of the diaphragm.

Many cases of food deficiency are of mixed type. Symptoms attributable to scurvy or to pellagra are frequently associated with those of beriberi. Among the well known mixed forms of vitamin deficiency are ship beriberi and Rand scurvy. Although the relationship of nutritional oedema to beriberi is in doubt, some of the cases of this disease in India have shown mild neuropathic symptoms or cardiac dilatation which could be ascribed to beriberi. The "chachaleh" of British Somaliland, as described by Buchanan (1932) has some features suggesting beriberi, but it seems to be more closely related to pellagra.

According to Jolliffe (1940) and R. D. Williams et al (1940), early thiamin deficiency may cause a variety of symptoms which are commonly labeled neurasthenia.

Infant beriberi is likely to appear in breast-fed infants of mothers whose diet is deficient in vitamin B-1. The mother may or may not show signs of beriberi. The symptomatology in the infant differs considerably from that of beriberi in the adult. Hoobler (1928) has well described the disease as seen in the Philippine Islands and also the milder types, which he believes are common in the United States.

Vomiting, constipation, anorexia, loss of weight, fretfulness and pallor are among the early symptoms. Vomiting is considered a grave symptom. The cry becomes feeble and plaintive and the tone altered in a peculiar manner. The altered cry has been attributed by some writers to pressure on the left recurrent laryngeal nerve by a dilated auricle. Others have ascribed it to a lesion of the nerve itself. During acute attacks of colicky pain, the body and limbs become rigid and there may be cyanosis. Opisthotonos or convulsions may occur. There may be slight signs of meningeal irritation, but the spinal fluid shows no abnormality. The muscles,

particularly those of the calves, are apt to be hypersensitive and the knee jerks diminished, but there is usually little clear evidence of neuropathy.

The course of the disease in infants tends to be rapid and the mortality used to be high. Death is preceded by increasing tachycardia, oedema and congestive heart failure. Lymphopenia is said to be common in infantile beriberi.

Diagnosis

An early case of beriberi may appear to be well nourished. Beriberi should be considered as a possible diagnosis in cases of motor and sensory neuropathy in which the peripheral nerves are chiefly involved and also in cases of oedema or cardiopathy which do not clearly belong in other categories. The diet in such cases should be scrutinized carefully. Because there are no positive diagnostic criteria, a diagnosis of beriberi requires exclusion of other diseases which can cause neuropathy, oedema, or circulatory abnormalities. Among such diseases are tabes dorsalis, pellagra, nutritional oedema, nephritis, and various kinds of myocardial diseases. Triorthocresyl phosphate poisoning ("ginger" or "jake" paralysis) causes a flaccid form of motor paralysis. The possible significance of this and of other neurotoxic chemicals should be borne in mind when the diagnosis is in doubt.

Evidence of a recent attack of diphtheria which has been inadequately treated should suggest diphtheritic paralysis. Early paralysis of the soft palate, extension of the neurological signs downward, and lack of sensory disorders characterize most of the cases of diphtheritic paralysis. Arsenical paralysis may closely simulate beriberi. Lead palsies, as a rule, are easy to recognize.

Even when a case of neuropathy has been ascribed to diphtheria, to one of the heavy metals, or to some other recognized neurotoxic agent, it is still possible that deficiency of vitamin B-1 or defective utilization of this vitamin may play a significant etiological role. Some of the neuropathies occurring in diabetes may be traceable to vitamin deficiency. There are also indications that deficiency of vitamin B-1 is an important factor in Korsakoff's syndrome, in some cases of Landry's paralysis and, probably also, in Wernicke's syndrome. Vitamin B-1 deficiency may prove to be significant in some of the other diseases of the central nervous system which are not ascribable to inflammatory processes, to arteriosclerosis, to hereditary influences, or to the known neurotoxic agents.

Among the conditions which may lead to beriberi as a sequel are dietary fadism, unwise and prolonged therapeutic restriction of diet, chronic alcoholism, pregnancy and lactation, hyperthyroidism, malnutrition incidental to severe infectious disease, to chronic wasting disease, cirrhosis of the liver, or to certain operations on the gastro-intestinal tract. When neurologic lesions develop in connection with any of these conditions, vitamin B-1 deficiency should be considered as a possible cause.

The therapeutic test based upon administration of adequate dosage of thiamin over a period of ten days undoubtedly has diagnostic value in

cases of beriberi having disorders of the circulation or of the digestion. It can not be recommended for diagnosis of cases in which evidence of neurological lesions predominates.

FIG. 230.—Characteristic position of feet in atrophic beriberi. (After Werner.)

Studies of the urinary excretion of thiamin (Robinson et al: 1940), indicate that under properly controlled conditions the level of the urinary

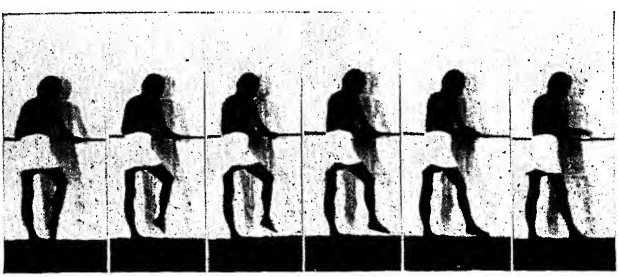

FIG. 231.—Gait in atrophic beriberi. (From Ruge, Mühlens and zur Verth.)

excretion of thiamin permits an obective determination of the state of thiamin nutrition in the human subject; and that patients who have sub-

sisted on a diet which is deficient in thiamin, excrete a smaller percentage of a test dose of thiamin than do persons whose diets have been adequate in thiamin.

It has been suggested that the determination of the amount of blood pyruvic acid may be of value in diagnosis. However, actually this is of little value in the diagnosis of the disease itself though it may be of some interest in measuring the severity of the infection and pyruvic acid is increased especially in severe fulminating or advanced cases. Eddy and Dalldorf (1941) have employed the method of Platt and Lu for this purpose. Values above 1.30 mgm per cent are considered abnormal.

Prognosis.—Death is to be expected in fulminating cases of beriberi, whether in adults or in infants. In the less acute cases, deaths are frequent unless adequate treatment is applied promptly. The prognosis is better in cases in which neurologic symptoms predominate and in which circulatory disorders have not appeared. Permanent disability may result from irreparable damage to the nerves if recovery is long delayed through failure to recognize the condition or to provide adequate treatment

Prophylaxis

Diets which contain large proportions of starches or of starches and sugars should be supplemented by foods containing ample quantities of vitamin B-1. Under conditions which are known to require increased amounts of this vitamin, the vitamin component of the dietary should be high.

In countries or localities where polished rice is the principal food of large numbers of people, its use should be discouraged by appropriate legislation. Undermilled rice, barley and oatmeal are excellent substitutes. During the winter months, when poor families such as those of the fishermen of Newfound are likely to subsist chiefly on white flour and salt pork, efforts should be made to provide them with the vitamin-containing foods or with vitamin concentrates. The dietaries of ships on long voyages, of prisons, asylums, garrisons and labor camps, should be so planned as to provide the necessary accessory food factors.

Bread made from whole wheat flour contains much vitamin B-1 whereas white bread contains little, if any. Where maize is the staple, the meal used should contain the germ of the grain. Excessive refinement, as in the case of white wheat flour, removes the vitamin-containing germ. Some of the canned foods and especially those which are acid, are said to retain much of their original content of vitamin B-1.

Methods of cooking fresh meat and fresh vegetables require attention. Prolonged boiling is likely, through heat and oxidation, to destroy vitamin B-1. Considerable amounts of it are dissolved in the water in which vegetables have been boiled. Ordinarily, this water is thrown away. It should be added to soup. Cowgill (1939 a) believed that "American dietaries as a whole are unsatisfactory with respect to the content of vitamin B-1" and that it would be advantageous to add this substance to staple American foods.

In the many diseases or conditions which predispose to beriberi, the danger should be foreseen and preventive measures should be adopted. More attention should be directed to the prevention of mild states of suboptimal nutrition or of partial deficiency. Doubtless they are common in the United States and in Europe as well as in the tropics.

The possibility that the thiamin content of soils and of fertilizers may be significant in relation to the food value of crops has been suggested

by Williams and Spies (1938). The relationship of soils to nutrition has been discussed by Auchter (1939). Knowledge of this kind may prove to be of great value in the prevention of beriberi.

Treatment

General.—When beriberi is considered as a possible diagnosis, the patient should remain strictly in bed. This precaution is vital in early or acute cases lest serious circulatory symptoms should supervene. Cardiac "stimulants" are of little value for the circulatory disorders of beriberi. Venesection may be beneficial in cases of acute congestion. Distention is to be avoided. Foods should be taken in small amounts and at more frequent intervals. When there is much oedema, the fluid intake should be limited. Adequate treatment by diet and vitamin concentrates usually results in rapid elimination of the fluid by diuresis. The diet should be of high caloric value and should contain an abundance of all essential food elements including those of the vitamin B-complex as a whole. Cases which have neurological lesions of the limbs recover slowly. Meanwhile, the development of contractures must be prevented. Opiates may be needed for severe neuritic pain.

Vitamin B-1.—At first, a considerable excess of vitamin B-1, as compared with the normal requirement (p. 1054), should be administered in the diet or otherwise. It is important, also, to provide an abundance of the other vitamins and accessory food factors because more or less deficiency of some of these substances is likely to coexist.

Serious circulatory symptoms may develop rapidly, even in mild cases of beriberi. Therefore, it is safer to administer a vitamin concentrate from the outset rather than to trust to diet alone. The concentrate used should be of standard quality and of known unit strength. The International Unit is more often referred to in recent literature than is the Sherman Unit. The International Unit has been considered as equal in terms of vitamin activity to from one to three or even four Sherman Units.

Among the vitamin concentrates used to supplement the diet are extracts of rice polishings or of wheat bran, and dry powdered brewers' yeast which has not been autoclaved. Autoclaved yeast contains vitamin B-2 but not vitamin B-1. The unit strength of the various commercial preparations of yeast differs markedly.

Beneficial effects resulting from the administration of vitamin B-1 are to be expected only when the symptoms are due to a deficiency of this vitamin. Appetite may return promptly, digestive disorders may abate, and circulatory symptoms may show rapid amelioration. Oedema and cardiac enlargement may disappear. The response of infants to vitamin concentrates may be dramatic.

Neurological symptoms respond but slowly, particularly in cases of long duration. McGee (1939) believed that the rate of cure of "polyneuritis" in alcoholics was determined by the duration of the symptoms rather than by the dosage of vitamin B-1. Dr. Madelaine R. Brown

(personal communication), expressed doubt as to the advantages of using thiamin or even vitamin concentrates in cases of peripheral neuropathy in alcoholics, provided that the patient could take an adequate diet. All are agreed that improvement of symptoms which are clearly due to degenerative lesions of the nerves in beriberi is very gradual under any known form of treatment. Inasmuch as repair of nervous structures is ordinarily a slow process, it is doubtful whether rapid recovery can ever be achieved.

Dosage.—Strauss (1938) has recommended, for the mild type of case, that 30 grains (2 Gm.) of powdered brewers' yeast of good potency be taken thrice daily. Definitely diagnosed cases of beriberi were treated with pure, crystalline vitamin B-1 (thiamin) by intramuscular or intravenous injection in the daily dose of 20 to 50 mg. for a fortnight. Thereafter, oral administration in the same dosage was employed, or, if the injections of thiamin were continued, the dose was reduced to 10 mg. daily. Aring and Spies (1939) recommended for an adult a diet providing 4500 calories and rich in vitamin B-1. They supplemented the diet by administration of dried brewers' yeast (6 oz. or 170 Gm. daily), or extract of rice polishings (tikitiki) (3 oz. or 85 Gm. daily), or crystalline vitamin B-1 (10 mg. twice daily). They believed that, in severe cases of beriberi, 20 mg. should be administered and that in cases of mild deficiency, doses of 5 mg. daily are adequate. When there is reason to suspect that absorption of vitamin from the intestine may be impaired, and probably also in diseases of the liver, injections of thiamin are to be preferred to oral administration of thiamin or of concentrates.

According to Strauss (1938), overdosage with crystalline vitamin B-1, even when employed intramuscularly or intravenously, entails no harm. However, Narat and Loef (1937) have reported the presence of "depressor substances" in vitamin B-1 concentrates and even in a crystalline preparation of vitamin B-1. Their experiments were performed on dogs and rabbits. Caution may be advisable in the intravenous use of thiamin in the presence of severe circulatory disorders of doubtful nature. Nevertheless, intravenous injection is the method of choice for treating acute and alarming circulatory disorders which are caused by deficiency of vitamin B-1.

In moribund cases of beriberi, with circulatory failure, Hawes (1938) has observed astonishingly rapid improvement after (intravenous ?) injection of huge doses of "pure vitamin B-1." He injected, in some of his cases, 2000 I.U. at a single dose. When too small a dose was given, the benefit was transitory and was followed by collapse. The effect of a single adequate dose was lasting. Toxic effects were not observed.

Because of widespread and increasing enthusiasm for the use of vitamin B-1, it is well to remember that not all degenerative diseases of the nervous system are due to deficiency of vitamin B-1. The combined degeneration of the cord which occurs in pernicious anaemia and the lesions of the cord and brain seen in pellagra seem not to be appreciably benefited by administration of vitamin B-1.

Vitamin B-1 Content of Foods

Using the rat-growth method of assay, Booher and Hartzler (1939) have recently determined the vitamin B-1 content of many common foods. Their results were expressed both in international units and in milligrams of thiamin for the edible portion of the food as prepared for cooking or for table use. The foods tested were classified as follows:

Excellent (150 International Units or more per 100 Gm.)		
Beans, lima, dried	Peanut germ	Pork, ham, smoked (lean portion)
Cowpeas, dried	Peanut skins	Soybeans, fresh, green and dried
Oatmeal, "quick cooking"	Peanuts, whole, raw	
Oats, rolled	Pork chop (lean portion)	
Good (100 to 150 International Units per 100 Gm.)		
Beans, lima, green	Milk powder, skim	Rye, whole
Beans, navy, dried	Milk powder, whole	Walnuts, Persian (English)
Corn meal, white	Peas, green	Wheat, whole
Egg yolk		
Fair (30 to 100 International Units per 100 Gm.)		
Asparagus	Corn, sweet	Pineapple
Beef, lean muscle	Kale	Potatoes
Broccoli	Lamb, lean muscle	Prunes, dried
Brussels sprouts	Liver	Spinach
Cauliflower	Mustard greens	Sweet potatoes
Chicken, dark meat	Okra	Turnip greens
Corn meal, yellow	Peanuts, roasted	Wheat, shredded
Poor (less than 30 International Units per 100 Gm.)		
Apples	Fish, halibut	Onions
Bananas	Fish, salmon, red, canned	Oranges
Beans, green snap	Fish, trout, fresh-water	Peaches
Beans, yellow, wax	Flour, wheat "straight milled"	Pears
Beets	Flour, patent	Plums
Blackberries	Grapefruit	Raspberries, black
Cabbage	Lettuce, head	Raspberries, red
Carrots	Milk, condensed	Rhubarb
Celery	Milk, evaporated	Rutabagas
Cheese	Milk, skim	Sauerkraut
Chicken, white meat	Milk, whole	Squash
Cocoa	Molasses	Strawberries
Corn flakes	Muskmelon	Tomatoes, red
Egg white		Turnips

The vitamin B-1 content of ordinary diet can be enriched by adding to soup, either barley or the water in which vegetables have been boiled; by eating vitamin-rich cereals such as oatmeal, or barley; by using whole-

wheat bread; and by replacing some of the ordinary meats with liver, kidneys, or other glandular organs. Most of the vitamin B-1 content of eggs is in the yolk. The legumes are relatively rich in vitamin B-1, even when dried. Although rich in other vitamins, fresh cow's milk is relatively poor in vitamin B-1. Infants fed on cow's milk should, therefore, take a concentrate of vitamin B-1.

As to canned foods, it has even been stated* that "commercially canned foods may be depended upon to supply vitamin B-1 to extents proportional to the amounts of the vitamin originally present in the raw materials from which they were prepared."

The Council on Foods of the American Medical Association (Rose: 1940) has reported on the effects of refrigeration and cooking (p. 1359) as follows:

"Losses in vitamin B-1 (thiamin) content of quick-frozen foods are due to the preliminary blanching or to cooking for the table rather than to the refrigeration. Thus Rose and Phipard found no loss of vitamin B-1 in frozen peas as compared with the same peas fresh and uncooked, but there was a loss of 26 per cent brought about by cooking fifteen minutes, no cooking water being discarded. An even greater loss in short time cooking has been reported by Munsell and Kifer, namely a depreciation of 50 per cent in cooking broccoli for fifteen minutes. Fellers, Esselen and Fitzgerald have reported practically no loss of vitamin B-1 in frozen peas and little in spinach (8 per cent), but in the case of lima beans and asparagus the differences between fresh and frozen averaged 54 and 26 per cent respectively. The order of loss appears to vary with the blanching time, indicating again that cooking rather than freezing is responsible for the change."

Vitamin B-1 Requirements.—The Technical Commission of the League of Nations Health Commission recently estimated the human requirement for vitamin B-1. The Report (1938) said that: "An allowance of 10 international units per 100 calories of food-intake seems to be adequate. This allowance would place at 300 international units the daily requirement for an adult of 70 kilogrammes body-weight receiving a diet of 3000 calories." It was further recommended that the diets of pregnant and lactating women should contain two to three times the amount of the minimal daily requirement (i.e. 600 to 900 units); that infants should receive 10 to 15 international units per 100 calories of food-intake; and that 200 to 250 international units be allowed for nursery-school children. These recommendations closely approximate those of Cowgill (1938).

Pharmacology of Thiamin.—The heat-labile part of the vitamin B-complex which is known to be important for man is vitamin B-1. In its chemically pure crystalline form it is called thiamin or aneurin.

Thiamin is usually prepared and administered as the hydrochloride (also called chloride or crystalline vitamin B-1 hydrochloride). In solution, thiamin is acid. It can be sterilized at 120°C. because heat has little effect upon it except in neutral or alkaline solution (Williams: 1939).

* *Nutritive Aspects of Canned Foods. American Can Company.* 1937.

Thiamin crystals absorb water on exposure to air, and they are very soluble in water.

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Chapter XXXIV

PELLAGRA

Synonyms.—Psilosis pigmentosa; Mal de la rosa; Mal del sole; Alpine scurvy; Chichism (northern South America).

Definition.—Pellagra is now believed to be a nutritional disease in which there may be deficiency of more than one component of the heat-stabile portion of the vitamin B-complex. Still other deficiencies coëxist in many cases. There is no clinical ground for distinguishing "endemic" from sporadic cases of pellagra.

Typical and advanced cases of pellagra are characterized by three groups of symptoms: a peculiar form of dermatitis; digestive disorders with or without diarrhoea; and psychoses of the confusional type.

History.—Credit for the first description of this disease is usually given to Casal who saw it in Spain in 1735. His paper was not published until 1762. Frapolli named the disease pellagra in 1771. After 1810, and for a hundred years, the belief was widely held that pellagra was caused by eating maize. Those who supported the maize theory were called zeists. *Zea mays* is the scientific name for maize or "Indian corn." The well known researches of Goldberger paved the way for the concepts of pellagra which are current today. Infection is generally regarded now as a contributory factor in some cases but not as a primary cause of pellagra. As late as 1930, some still believed pellagra to be an infectious disease.

Geographical Distribution.—Pellagra has been common in Italy, Spain, Portugal, the Balkan States, Greece and Turkey. There were about 100,000 cases in Roumania in 1906. The incidence of the disease in Italy has been decreasing for a long time. In 1910 there were only 33,869 cases reported there, as against 104,607 cases in 1881.

In Egypt, pellagra was first recognized by Sandwith in 1893. It has been widespread in Lower Egypt but rare in Upper Egypt, where the people eat millet instead of maize. It occurs also in Algeria and in other parts of Africa. Probably pellagra is common in India, the Straits Settlements, China, Japan, and the West Indian Islands. It is common locally in Mexico and in parts of South America.

After the recognition of pellagra in the United States by Babcock in 1907, the disease was found to be very prevalent in the southeastern states. During the past 10 years, cases have been discovered in many other parts of this country. Doubtless isolated cases could be found in almost any part of the world.

Incidence.—Pellagra may appear in persons of any race, at any age, and in either sex. In some localities it is more common in males than in females or vice-versa. Pellagra is said to be rare in infants but common

in young children. The local incidence of pellagra depends largely on the economic status and consequent dietary habits of the population. In those parts of Europe and of the United States where the general economic level is low and where maize is the staple food of the poor, large numbers of cases of pellagra have occurred. There have also been outbreaks in asylums and in camps when the dietary was inadequate in vitamins.

Contributory or secondary factors, including infectious diseases, may influence the incidence of pellagra at a particular time or place. In the United States, new cases of pellagra may develop at any season but they appear most frequently during the early spring.

Etiology

When one compares the evolution of knowledge about their etiology, a striking parallelism is revealed between the history of beriberi and that of pellagra. Both have been attributed in turn to specific articles of diet, to toxins of doubtful nature, and to a variety of infectious organisms. Both diseases are now ascribed to deficiency of vitamins. The primary and essential cause of pellagra seems to be deficiency of components of the heat-stabile portion of the vitamin B-complex. Deficiency may be brought about by inadequate ingestion or decreased absorption or, probably, by disorders of metabolism which might interfere with utilization of vitamins after absorption. Among the contributory causes of pellagra are the acute or chronic infectious diseases, particularly those associated with diarrhoea, the chronic wasting diseases, chronic alcoholism, pregnancy and lactation.

Sydenstricker et al (1936) offered the hypothesis that, along with deficiency of an extrinsic factor, there is more or less deficiency of an intrinsic factor as well. They believed that some individuals retain enough of the intrinsic factor to recover even on an inadequate diet; that others regenerate it rapidly when treated with an abundance of the extrinsic or dietary factor; and that still others, totally lacking in the intrinsic factor, are unable to regenerate it even under optimum dietetic therapy. Even in the absence of the intrinsic factor, patients may recover under substitution therapy. A possible relationship between pellagra and disturbed liver function or failure of a diseased liver to store the required vitamins, has also been postulated by Sydenstricker et al (1939).

Milk, meats, and dried brewers' yeast contain the heat-stabile portion of the vitamin B-complex, which was formerly called vitamin B-2, or vitamin G. Further study showed that vitamin B-2 contains various different substances which are important for the nutrition of man or of animals (p. 1036). At this point, confusion as to nomenclature arose. The literature indicates that such terms as vitamin B-2 and vitamin G have meant different things to different authors. These terms, therefore, should be dropped. The term Vitamin B-2 complex will be used here to designate the group of heat-stabile components of the Vitamin B-complex.

The vitamin B-2 complex includes nicotinic acid and riboflavin which have proved to be important for nutrition in man. It contains also

vitamin B-6 and pantothenic acid. It is generally recognized now that deficiency of nicotinic acid (p. 1036) is an important cause of some of the symptoms of pellagra. The situation with regard to riboflavin is less clear. The significance for man of vitamin B-6 is uncertain (p. 1037), and that of pantothenic acid is still obscure.

Pellagra appears now to be a syndrome caused by deficiency of more than one fraction of the vitamin B-2 complex. The varied symptomatology and the occurrence of atypical cases can be attributed to differing

FIG. 232.—Dry dermatitis on face, hand, neck and upper chest. Egyptian case. (From Lavinder and Babcock.)

degrees of deficiency of the several important components of the vitamin B-2 complex and to the lack, in some instances, of other substances essential to nutrition. Among these other factors which complicate the picture rather frequently are deficiency of vitamin B-1, of iron, or of protein.

Nutritional disorders apparently allied to pellagra but showing divergent symptomatology, have been reported from Africa by Stannus (1936) and by subsequent authors (Trop. Dis. Bull: 1936; vol. 33; nos. 11 and 12; pp. 815 and 885).

Exposure to direct sunlight tends to aggravate or to produce skin lesions on exposed surfaces. The increased sensitivity of the skin to sunlight is manifested during the active stages of pellagra. It has been

ascribed to the existence of photodynamic substances circulating in the blood. Porphyrin (p. 1060) was incriminated by Bassi (1934), but Anderson and Ayres, Jr. (1934) believed that the hypersensitivity is related to disturbed sulphur metabolism and through this to amino acids and perhaps also to the vitamins. Similarly, the skin of pellagrins is said to be abnormally susceptible to injury by x-rays. The lesions seen occasionally on the genitalia appear to be irritative phenomena caused, perhaps, by

FIG. 233.—"Butterfly" eruption on face of child two years old. (Deaderick and Thompson.)

substances excreted through the skin. The dermatitis seen in some cases on the elbows and knees might be attributed to the effects of friction against the bed-clothes acting upon an abnormally sensitive skin.

Pathologic Physiology

Turner (1931) reported the following findings: (*a*) Plasma volumes, 32 per cent above and 68 per cent below normal; (*b*) Red cell volumes, 5 per cent above and 95 per cent below normal; (*c*) Total blood volumes, 17 per cent above and 82 per cent below normal.

Indicanuria has long been recognized as a frequent occurrence. It has been attributed to increase of the putrefactive process in the intestine.

James H. Smith (1931) has advanced some important concepts regarding the skin lesions of pellagra. He said: "An adequate supply and a normal metabolism of sulphur appear to exert a protective influence against the pathologic effects of solar irradiation. The evidence suggests that an inadequate supply of sulphur as cystine is an important cause of pellagra, and that the abnormal metabolism of sulphur is an important feature of pellagra."

Although albumen and casts are present in the urine in about 50 per cent of cases of pellagra, renal disorders are not characteristic of the disease (Sullivan, Stanton and Dawson: 1921).

Several recent writers have reported excess of porphyrin, or of "porphyrin-like pigment" in the urine of pellagrins. Meiklejohn and Kark (1939), discussing the test for porphyrins as used by Beckh, Ellinger and Spies ("B.E.S. Test") offered a different interpretation of its meaning. They said: "it would seem more proper to refer to the B.E.S. test as indicating the presence of pigments capable of producing the urorosein reaction rather than to refer to such pigments as porphyrin-like substances, which they in no manner resemble."

Campbell and Shaver (1937) reported that the blood of pellagrins reduces iodine solutions at a constantly greater rate than does the blood of normal or of diseased control patients. They believed that this reaction might be of value for diagnosis.

Hypersensitiveness to insulin has been reported as occurring in pellagrins. Mainzer (1939) has attributed it to disease of the adrenals with consequent disturbance of carbohydrate metabolism.

Pathology

The pathology of pellagra is neither constant nor characteristic. Lynch (1932) said that the structural changes of pellagra are primarily degenerative but may become irritative or even inflammatory in character. These changes may be widespread in the surface epithelium of the skin and in the mucosa of the alimentary tract, or in the nervous system Emaciation, which is usually pronounced and which may become extreme, is very constant. Atrophic changes may be found in all the tissues, and in any organ.

Skin.—A dermatitis, associated with patchy or diffuse pigmentation, usually occurs on surfaces exposed to light. It is most common on the backs of the hands and on the cheeks. It may be seen on the back of the neck or over the upper part of the sternum. Erythema precedes pigmentation. Similar skin lesions are seen on the dorsal surfaces of the feet, on the shins, and on the forearms of those whose clothing does not cover these parts. Dermatitis with thickening of the epidermis and erythema sometimes appears on the elbows and on the knees, especially in bed-ridden patients. Erythema, or increased pigmentation and dermatitis, may be found also on and about the genitalia or the anus. The histological

changes in the skin, the mouth and the oesophagus were described in detail by Denton (1925).

Gastro-intestinal Tract.—The most frequently observed of the gastro-intestinal lesions in pellagra is glossitis, with or without stomatitis. Superficial ulceration follows in some cases and secondary infection may occur. Similar lesions may be found in the oesophagus, in the stomach, and in the small or, more often, in the large intestine. The wall of the intestine may be abnormally thin. The liver and the spleen usually show atrophy. The liver frequently exhibits fatty degeneration. The viscera may be pigmented. The heart may show fatty degeneration or brown atrophy and fibrosis. The adrenal glands are frequently diseased.

Nervous System.—Lesions of the nervous system have been demonstrated in the brain, the cerebellum, the medulla and pons, the cord, and the peripheral nerves. The distribution of the lesions is extremely variable. Damage to nerve structures is seldom visible except under the microscope. Lynch believed that still other neurological lesions may exist which are not demonstrable by available technics but which can give rise to symptoms.

Among the gross changes which have been found in the nervous system in pellagra, are oedema or wasting of the brain, excess of fluid in the ventricles, and extensive degeneration in various parts of the cord. The distribution of the cord lesions is so variable, both as to the structures chiefly involved and as to the level of the more pronounced pathology, that general statements are of little value. Probably, the principal lesions of the cord occur most frequently in the cervical and lumbar regions and in the crossed pyramidal tract, in the posterior tract of Goll, and in the fibers of the posterior roots. The anterolateral tract seems to be involved less often. The tract of Burdach and the direct cerebellar tract usually escape.

Frequently, the nerve cells of the anterior and of the posterior horns in the spinal cord show degenerative changes. The corresponding cells in the medulla and pons, the pyramidal cells of the cerebral cortex and the cells of Purkinje in the cerebellum may show similar changes. Langworthy (1931) found pigment deposits in the "cells of the sensory and autonomic ganglia and those in the spinal cord and brain-stem." . . . "The small cells of the sensory ganglia showed the greatest deposit of pigment." Similar lesions of the brain and of the sympathetic ganglia have been reported by others.

Symptoms

Course.—The usual course of pellagra is subacute or chronic but acute cases occur and relapses are common. The duration of the disease varies from weeks or months to many years.

The first symptoms noted by the patient are apt to be skin lesions resembling sunburn, or digestive disorders, or both. Less often, mental disorders are among the early signs of pellagra. As a rule, their appear-

ance follows that of other signs. Increasing weakness, loss of weight, and redness and denudation of the tongue are usually associated with the other signs of the disease.

Ordinarily, the temperature in pellagra is subnormal, normal, or but slightly elevated. In fulminant cases, the temperature may be high. Anaemia, when present, is usually of moderate severity. The cell volume is generally decreased, but it may be increased. Leukopaenia with relative increase of lymphocytes is to be expected. Hydrochloric acid may be diminished or absent from the gastric secretion even after administration of histamine. The digestive ferments and the quantity of gastric juice are said to be decreased. Abnormalities in the spinal fluid are not seen in typical cases. Individual cases rarely exhibit all the common symptoms of pellagra.

Skin.—The distribution and general character of the skin lesions have been described under Pathology (p. 1060). The lesions are strikingly symmetrical. Ordinarily, those on the hands are sharply delimited at the wrist and do not extend to the two distal phalanges. The dermatitis on the face is less circumscribed than that on the hands. It involves especially the malar prominences chiefly, and the bridge and the sides of the nose. The forehead and the anterior aspect of the chin may be affected. The skin lesions follow a sequence of development beginning with erythema, with or without slight oedema. This stage is succeeded by thickening and roughening of the epidermis and by a dirty-looking pigmentation. In the more acute cases, vesicles may appear. Usually, patchy exfoliation of the skin leaves depigmented areas in which the new skin appears to be atrophied. Sometimes there is a pigmented area which extends from the sternum around the back of the neck and onto the mastoid processes. The lower margin of pigmentation may be sharply defined, whereas the upper border merges gradually into the normal skin of the scalp. In some cases a line of pigmentation encircles the neck.

The lesions which occur on the elbows and knees show redness, thickening and exfoliation with little or no pigmentation. They have some resemblance to psoriasis. On the scrotum, the vulva and in the region of the crotch, there may be patches of dermatitis with redness or increased pigmentation. There may also be balanitis, vaginitis, or urethritis. The milder skin lesions cause little discomfort and they may not be noticed by the patient. More severe lesions are associated with sensations of burning and itching. Pigmentation persists for a long time after recovery from the dermatitis. The nails may be atrophic and brittle or deformed.

The skin lesions in the Negro show increased black or purplish pigmentation. Those in olive-skinned persons are dark, reddish-brown.

Not infrequently, one sees on the sides of the nose, a yellowish, granular, dry substance which protrudes like little horns from the mouths of the sebaceous glands. Similar lesions may sometimes be seen on the chin. "Angular stomatitis" and cheilitis (cheilosis) are not uncommon in pellagra. Recently several authors have attributed these lesions and also certain lesions of the eyes to riboflavin deficiency (p. 1036).

The group of digestive symptoms includes sensitiveness of the tongue and buccal mucosa, burning pain over the oesophagus and in the epigastrium, loss of appetite, eructations, flatulence, colic, vague abdominal distress and diarrhoea or constipation. Attacks of diarrhoea may alternate with constipation. Denudation of the epithelium of the tongue is apt to be especially marked at the tip and along the edges but the whole tongue may be bright red, rough and fissured. The buccal mucous membrane may share in the process, and superficial ulceration may develop. The pyrosis and epigastric pain which succeed the taking of food may be so severe that the patient fears to eat.

Nervous System.—The neurological picture in early cases is ill-defined and the symptoms may be transitory. Headache, vertigo, cramps in the muscles, backache, shooting pains in the limbs, and sleeplessness and "neurasthenic" symptoms are common. Coarse tremor of the hands, burning pains in the palms of the hands or soles of the feet, and paresthesia, or formication are frequently experienced. In advanced cases, the picture is usually that of spastic paraplegia with ataxia and increase of the deep reflexes. Romberg's sign, Chvostek's sign, tremor of the hands, or ankle clonus may appear and, finally, contractures may develop. Epileptiform attacks of cortical type or somnolence have been observed. In cases in which the knee jerks are diminished or absent, deficiency of vitamin B-1 may be a factor.

The early mental symptoms of pellagra resemble those of neurasthenia. More definite psychoses appear later. They may simulate manic depressive insanity, general paresis or senile dementia. Hypochondriasis or melancholia may lead to suicide. Hallucinations or maniacal attacks may occur. In cases of long duration, the insanity may become incurable. Increasing weakness and muscular incoördination ultimately render the patient helpless. Having reached a condition of extreme emaciation, he dies of exhaustion or of intercurrent disease.

Lesions of the cranial nerves occur occasionally in pellagra. Among them, retrobulbar neuritis seems to be relatively frequent. It appears early. Lesions of the facial nerves or of the ocular muscles, optic neuritis, toxic amblyopia or nystagmus may be caused by deficiencies of components of the vitamin B-complex. They may, however, be more depend-upon deficiency of B-1 than upon lack of constituents of the B-2 complex.

Circulatory disorders are seldom prominent in pellagra but, in a study by Mainzer and Krause (1940) of 23 cases in Egypt, slight electrocardiographic changes were found in about three-fifths of the cases. In some of the cases, the changes disappeared rapidly after administration of nicotinic acid. The electrocardiac changes were not considered characteristic of pellagra, and some at least of them have been observed in beriberi. Tachycardia was most commonly encountered at the height of the disease and bradycardia during convalescence.

Infantile pellagra appears to be relatively common in China and in Africa. Cases tend to be atypical or mild. A great variety of local names have been applied to it. Signs suggesting pellagra are often com-

bined with evidences of deficiency of vitamin A, B-1, C, or D, or with lack of protein or iron. Oedema is a feature of some of these cases. Desquamative dermatitis may be extensively distributed on the body. The course of infantile pellagra may be relatively acute.

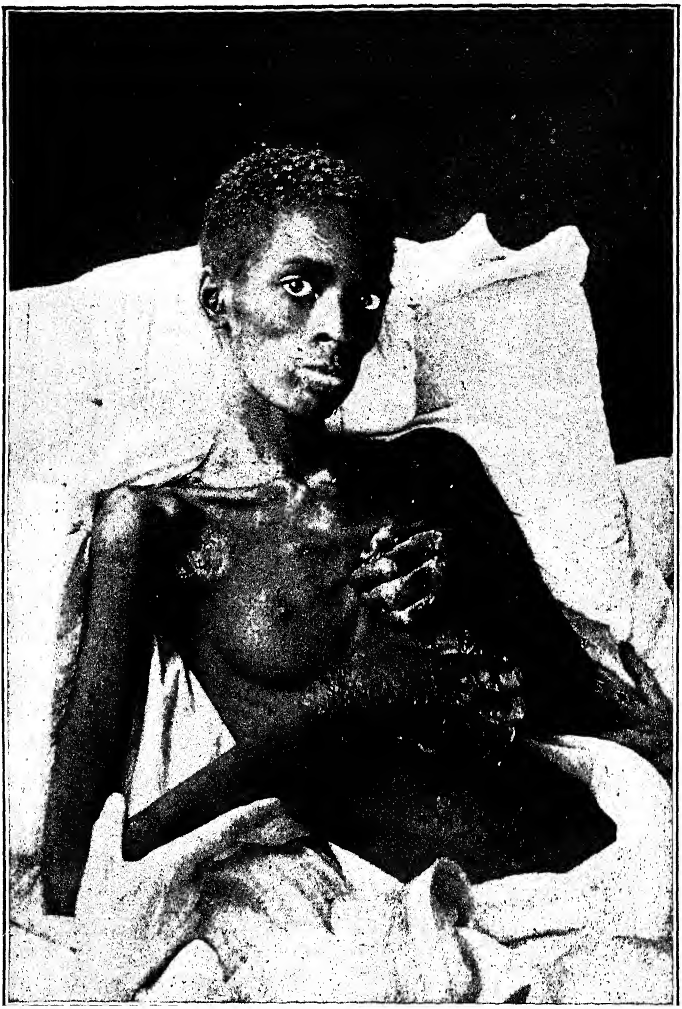

FIG. 234.—Wet dermatitis. Localization usual. Hands oedematous. Cachectic state. South Carolina case. (From Lavinder and Babcock.)

Atypical Pellagra.—Occasionally, soreness of the tongue only or mild gastro-intestinal discomfort or increasing weakness and loss of weight occur without characteristic skin lesions. These cases have been called "pellagra sine pellagra." Other cases may show features resembling sprue or pernicious anaemia. Sydenstricker (1940 b) said that protein deficiency

with resulting nutritional oedema is present in 15 per cent of the pellagrins seen in his clinic in Georgia and that anaemia due to iron deficiency is found in 35 per cent.

The syndromes of Korsakoff and of Wernicke may be associated with characteristic signs of pellagra. These syndromes are now attributed to deficiency of substances contained in the vitamin B-complex. It is possible that several other degenerative diseases of the nervous system are to be similarly explained (p. 1035).

"Pellagra typhus" is an acute form of the disease associated with high fever, delirium tremors, generalized rigidity, and convulsions. In cases of this type, the patient may appear well nourished. This condition is believed to be rare.

Subclinical pellagra has been described by Aring, Evans and Spies (1939) as follows: "Subclinical pellagrins are noted for the multiplicity of their complaints, among which are many that are usually classified as neurasthenic. The most common of these symptoms are fatigue, insomnia, anorexia, vertigo, burning sensations in various parts of the body, numbness, palpitation, nervousness, a feeling of unrest and anxiety, headache, forgetfulness, apprehension and distractibility. The conduct of the pellagrin may be normal, but he feels incapable of mental or physical effort, even though he may be ambulatory."

Mindus (1939), in a series of cases of gastric dysfunction of uncertain nature, found achylia or hypochylia in about 91 per cent. The clinical picture in his cases was characterized by anorexia, loss of weight, simple anaemia, insomnia, amenorrhea, hypesthesia, lassitude, muscular weakness, and anxiety, depression or apathy. Many of these patients responded well to treatment for pellagra.

Differential Diagnosis

There is no satisfactory test by which a diagnosis of pellagra can be confirmed. Diagnosis is easy in cases showing the more characteristic lesions of the tongue and of the skin. Nevertheless, many cases of pellagra have been erroneously ascribed in the past to sunburn, to ivy poisoning, or to various skin irritants used commercially.

Characteristic seasonal incidence, a history of a previous attack, or the recognition of other cases in the vicinity or in the population group to which the patient belongs, may help to establish an otherwise doubtful diagnosis of pellagra. The diagnosis may be further strengthened by a history indicating a background of dietary deficiency or of chronic alcoholism. Prompt response of the gastro-intestinal or mental symptoms to treatment with nicotinic acid, or rapid improvement of certain other lesions after administration of riboflavin is highly suggestive of pellagra. Responses to dietary treatment alone are less rapid. The vague symptomatology of subclinical pellagra should be borne in mind lest the patient be dismissed with a diagnosis of neurasthenia.

It should be remembered that pellagra may be combined with signs of deficiency of various other essential food factors; that it can develop as

a concomitant or sequel of a great variety of diseases in which the ingestion or assimilation of nourishment is seriously disturbed; and that mental disorders may be the first symptoms observed.

The nervous and mental symptoms of pellagra must be differentiated from those of vitamin B-1 deficiency, pernicious anaemia, general paralysis, neuro-syphilis, cerebral arteriosclersosis and senility. Usually, the neurologic lesions of pernicious anaemia resemble those of beriberi rather than of pellagra. The central neuritis described by Adolph Meyer, and Scott's palsy, (a form of central neuritis seen in Jamaica, Sierra Leone and Nigeria), have striking resemblances to pellagra. They may be etiologically related.

It seems probable that certain cases of chronic ulcerative colitis are dependent, at least in part, upon deficiency of components of the B-complex. The same may be true in some instances of poisoning by the heavy metals.

According to Barondes (1936), selenium poisoning in animals, or "alkali disease," resembles pellagra in that gastro-intestinal symptoms, nervous and mental disorders and dermatitis following exposure to bright sunlight are common to both. There appears to be a relationship between the toxicity of selenium and dietary defects. Thus, it seems possible that cases of selenium poisoning in man might be mistaken for pellagra.

Prognosis.—The mortality from pellagra has been high and sometimes very high in the past. Since the advent of modern methods of treatment, the prognosis has improved enormously. In general, recovery is to be expected not only in early cases but also in chronic cases with advanced emaciation and severe digestive disorders provided that adequate treatment is applied promptly. The outcome is uncertain, even with good treatment, in the presence of serious intercurrent disease.

Prophylaxis

Because the incidence of pellagra is intimately related to poverty and to the monotonous and inadequate dietaries which poverty may impose, the large-scale prevention of pellagra is partly an economic problem and partly one of education in the essentials of nutrition. Goldberger showed, years ago, that pellagra can be prevented by adding to an ill-balanced diet, sufficient quantities of fresh meat, milk and eggs; and that dried brewers' yeast also contained his pellagra-preventing or "P.P." substance.

As Sebrell has pointed out (1938), the prevention of endemic pellagra is simple in theory but difficult in practice. To this end, one should not forbid the ordinary and cheap foods of the locality, but should advise that they be supplemented by green, leafy vegetables, fresh or canned milk or buttermilk, lean pork instead of fat pork, canned salmon, haddock, and corned beef, poultry and rabbits (see also p. 1053). Home gardening should be encouraged in order to provide fresh vegetables. Powdered yeast or nicotinic acid may be distributed in the spring months when pellagra develops most often. Measures which reduce the incidence of chronic alcoholism are likely, also, to reduce that of pellagra.

Those in authority should guard against pellagra in labor camps, garrisons, prisons and asylums by assuring themselves that dietaries are adequate in pellagra-preventing foods. In the treatment of chronic diseases which interfere seriously with nutrition, the dietary should include milk, eggs, and fresh meat. When these cannot be taken in adequate amounts, the administration of brewers' yeast or nicotinic acid and riboflavin is indicated for prophylaxis.

Treatment

General.—Ambulatory cases of pellagra can be treated by rest and improved diet but it is well, also, to administer nicotinic acid.

When not exposed to direct sunlight, the skin lesions on uncovered surfaces show a striking tendency to disappear, even when the diet continues to be inadequate. It is difficult, therefore, to determine the effect on the skin lesions of dietary or of other forms of treatment. The effects of treatment for pellagra must, therefore, be evaluated largely on the basis of the response of symptoms relating to the gastro-intestinal tract or to the nervous system. After adequate treatment, improvement in the condition of the tongue and of the buccal mucosa and amelioration of the digestive disorders appear with considerable promptness. Symptoms referable to the nervous system respond more slowly, as a rule. An adequate diet, for those who can assimilate it, cures all the symptoms of pellagra. In severe cases of pellagra, or those of long standing, the digestive system may be unable to cope with an adequate diet even when administered in the form of liquids and soft solids. Sometimes, the administration of brewers' yeast causes diarrhoea or vomiting. Under these conditions, nicotinic acid (p. 1068) or liver extract should be used. The lesions which have been ascribed to riboflavin deficiency (p. 1036) may yield slowly or not at all to nicotinic acid, but they may respond quickly to riboflavin. Vitamin B-6 pantothenic acid and perhaps still other heat-stabile components of the vitamin B-complex (p. 1037) may yet prove to be important in the treatment of some of the symptoms of pellagra. It is important to administer to the patient all the necessary food factors by diet or otherwise. As in beriberi, so also in pellagra, conditions which increase the basal metabolic rate require larger amounts of the vitamins.

Nicotinic acid is ineffective as a remedy for nutritional cardiopathy or peripheral neuropathy. These conditions usually respond to thiamin (p. 1054).

The crude liver extracts used by mouth may relieve most of the symptoms of pellagra but the more refined preparations intended for injection seem not to contain all the substances required. According to Ruffin and Smith (1934), they may be beneficial for macrocytic anaemia, when present in pellagra. Ruffin and Smith (1937) have also expressed the view that liver contains two factors, both of which are necessary for the treatment of pellagra.

Hypochromic anaemia requires iron. When absent from the gastric secretion, hydrochloric acid can be prescribed advantageously by mouth. Good results have followed the use of ventriculin in cases in which the gastric secretion was defective.

All severe cases of pellagra require rest in bed and excellent nursing care. Special efforts are needed to ensure cleanliness and to prevent the development of bed sores and of contractures. Bland ointments and protective dressings are useful when the skin lesions are severe. The skin should not be exposed to direct sunlight until convalescence has become well established.

Diet.—The diet of the pellagrin should be of high caloric value (3000 to 4000 calories) and rich in all of the accessory food factors. In particular, the constituents of the vitamin B-complex as a whole should be supplied in abundance. To treat a case of pellagra with a single active constituent of the vitamin B-complex is to invite the development of manifest deficiency of other components of the complex.

Fresh milk, buttermilk, eggs, lean meats, liver and kidney are among the common foods which are particularly beneficial to pellagrins. To these foods should be added broths, fruit juices, and fresh, green vegetables. When the digestion is much disturbed, the patient may be able to take only liquids and soft solids. Feedings should then be administered at frequent intervals. Routine diets are to be avoided in severe cases of pellagra.

Yeast.—Brewers' yeast has been used extensively in the treatment of pellagra as a source of vitamins. Prompt and pronounced benefit following its use has been reported by numerous observers. It appears, however, that the various preparations available differ much in potency, and that no very satisfactory method of standardizing them has yet been devised (Rhoads: 1939).

Brewers' yeast is ordinarily pescribed in the form of a dry powder. The use of autoclaved yeast, which is lacking in vitamin B-1, probably should be limited to experimental purposes. Formerly, the usual dose of powdered yeast was 15 to 30 Gm. daily or about 3 to 6 level teaspoonfuls in divided doses. Doses of 75 to 100 Gm. daily are now being recommended. No deleterious effects aside from diarrhoea in some cases have been reported from such dosage of pure, dried yeast. Moist yeast cakes are not ordinarily used and compressed tablets are out of the question because adequate dosage can scarcely be given in this form. Powdered yeast can be stirred up with milk, eggnog, tomato juice, or warm water and salt, or it can be eaten with cereals. The daily dose should be divided into portions to be administered at intervals of a few hours.

Nicotinic acid is a pure, crystalline substance which can be made synthetically. It is present in considerable amounts in the foods which have proved beneficial for the prevention and treatment of pellagra, and is a constituent of the heat-stabile portion of the vitamin B-complex. Neither the maximal nor the minimal dosage of nicotinic acid has yet been determined. The optimum dosage varies greatly in individual cases.

Nicotinic acid has been administered by mouth in solution, in tablets or in capsules. In small numbers of cases it has been used by hypodermoclysis, intramuscularly or intravenously, dissolved in sterile physiological salt solution. Administration by mouth is, usually, the method of choice.

Aring et al (1939) recommended that at least 500 mg. should be administered daily by mouth in 10 equal doses. In extremely severe cases, they suggested dosage of 1000 mg. daily. They have used as much as 2000 mg. daily in divided doses without untoward results. In a comprehensive article on the treatment of pellagra, Spies, Bean and Stone (1938) reported excellent results in pellagra following the use of nicotinic acid, nicotinic acid amide, or sodium nicotinate by mouth. They state that 500 mg. daily in divided doses is usually effective, but that double dosage seemed sometimes more beneficial and that small dosage may give dramatic results.

Single doses of 200 mg. by mouth, or 10 mg. intravenously, very promptly produced flushing of the face and of the upper part of the trunk. This was associated with burning and itching sensations, increased activity of the sebaceous glands and sometimes with increased gastro-intestinal motility. Nausea, vomiting or abdominal cramps sometimes followed the taking of large doses. Nicotinic acid tends to increase the secretion of hydrochloric acid in the stomach.

Various authors have advised caution in the use of the larger doses of nicotinic acid until more is known about this drug. Prolonged use might have ill effects, thus far unknown, and reactions attributable to idiocyncracies may later be reported. The dosage for children should be roughly in proportion to body weight. Field Jr. and Robinson (1940) have given as much as 500 mgm. of nicotinic acid amide by mouth on an empty stomach without causing vasodilatation or any abdominal, cerebral or cardiac symptoms. Nicotinic acid amide is a normal constituent of the body whereas nicotinic acid is not. Therefore, use of the amide would seem to be preferable.

Spies, Bean and Stone (1938) used nicotinic acid intravenously in only two cases of the series then reported. One patient showed marked improvement after receiving 10 mg. daily for 4 days and another after taking 20 mg. daily for the same period.

In another article, Spies, Cooper and Blankenhorn (1938 a) reported having used 30 mg. of nicotinic acid in physiologic salt solution as a single dose administered intravenously at the rate of 2 mg. per minute, and as much as 80 mg. to a patient within several hours. To another patient, 100 mg. was administered in a liter of physiologic salt solution by infusion. Untoward symptoms did not occur. Probably, nicotinic acid should be used by the intravenous route only when the patient, because of vomiting, cannot take it by mouth.

In a number of cases of pellagra which were kept on a restricted diet and treated with nicotinic acid only, relapses have occurred. They have yielded to increased dosage. Other such cases have developed peripheral neuropathy while taking nicotinic acid. These observations serve to

emphasize the importance of a well balanced, high-vitamin diet for the treatment of pellagrins. They indicate, too, that substances other than nicotinic acid are lacking in pellagra.

According to Spies, Bean and Stone (1938), the administration of preparations of nicotinic acid to pellagrins causes pronounced improvement in most of the symptoms within 72 hours. The patient very soon experiences a sense of well-being, the lesions of the mucous membranes fade and show other signs of healing, the appetite improves, the digestive symptoms and diarrhoea decrease, the mental abnormalities abate and "porphyrinuria" diminishes or disappears. The skin lesions fade rapidly but the severer forms of dermatitis do not heal. Peripheral neuropathy is not relieved, but it yields to vitamin B-1. The lesions which have been attributed to riboflavin deficiency may yield to riboflavin after failure with nicotinic acid.

Cobb (1939) has emphasized the value of nicotinic acid not only for the psychoses of pellagra but also for those associated with acute or chronic alcoholism, with arteriosclerosis or with other signs suggesting senility.

Riboflavin, *Lactoflavin*, *Vitamin B-2 or G*, is one of the heat-stabile components of the vitamin B-complex. Flavin is found in many plants and, in some of them, it has been shown to be identical to riboflavin. In crystalline form, riboflavin is orange-yellow in color, slightly soluble in water and soluble in alcohol. It is resistant to mineral acids but sensitive to alkali. When dissolved in water, riboflavin is fluorescent. Riboflavin performs some functions related to "the oxidation processes of the cells" (Hogan: 1939). Other possible physiological functions of riboflavin remain in doubt. In certain animals, and probably in man, riboflavin (flavin) is stored in the liver, kidneys and heart. Rats on a diet inadequate in riboflavin, die from deficiency of this substance even though considerable amounts still remain in the organs. Riboflavin is excreted in the urine of man, however, even when the intake is deficient (Emmerie: 1936 and 1937). Riboflavin is excreted also in human milk and in the milk of cows. The amounts so excreted are influenced by the riboflavin content of the diet.

The lesions which have been attributed to riboflavin deficiency (p. 1036) by Sebrell and Butler (1939) and by Spies, Bean and Ashe (1939 a) are seen especially in cases of the type which has been called "pellagra sine pellagra." Some of them have been designated by the term "angular stomatitis." They are characterized by maceration of the skin or by vertical fissures at the angles of the mouth. Reddening, maceration, denudation, or transverse cracking of the lips is called cheilitis or cheilosis. In some cases also, seborrheic accumulations occur on the nostrils, around the nose and, less often, on the chin, on other parts of the face, or elsewhere on the body. The sebaceous glands appear to be plugged with a dry, horny substance which projects from their orifices. The neighboring skin may be darkly discolored.

Kruse et al (1940) have included in the picture of riboflavin deficiency a peculiar type of glossitis and certain ocular signs and symptoms. In

contrast to the fiery red color of the tongue of the pellagrin, they said that the tongue of riboflavin deficiency has a purplish-red or magenta hue. It is clean and the papillae are flattened. The ocular signs and symptoms include vascularization of the cornea, keratitis resembling that seen in syphilis, itching or burning sensations of the lids, more or less photophobia, and dimness of vision or partial blindness in poor light. These authors claimed that the lesions did not yield to vitamins A or C, thiamin, or nicotinic acid, but that they were cured with riboflavin. In some cases, they recurred after riboflavin had been withdrawn. On the other hand, several authors have reported cure by means of nicotinic acid (Stannus: 1940) of some of the lesions which have been ascribed to riboflavin deficiency. Further work may justify the separation of clinical pellagra into nicotinic acid deficiency, "ariboflavinosis," and perhaps other syndromes.

In a paper describing the ocular manifestations of ariboflavinosis, Sydenstricker, Sebrell and others (1940) said that these lesions develop early and that "ariboflavinosis" is possibly the most prevalent apparently uncomplicated avitaminosis." Elsewhere, Sydenstricker (1940 b) stated that recognition of superficial vascularizing keratitis depends upon examination with the slit-lamp.

DOSE.—Synthetic riboflavin has been used by mouth, subcutaneously and intravenously. No toxic effects have been reported. Neither the minimal effective dosage for therapeusis nor the maximal dosage have been determined.

A daily dose of 5 mg. by mouth has been used with success by Spies, Vilter and Ashe (1939); and Jolliffe et al (1939) have given 10 mg. daily by mouth. Sydenstricker et al (1939) have used with benefit single doses of 10 mg. and of 50 mg. subcutaneously, and of 10 mg. intravenously dissolved in 200 cc. of physiologic salt solution. In a subsequent paper, Sydenstricker (1940 a) considered 3 mg. to be the minimal dose by mouth and said that as much as 15 mg. might be required for rapid improvement. For specific effect, it is necessary to use the pure synthetic vitamin because it is difficult otherwise to secure adequate intake. He did not consider that suitable preparations for injection are yet available and he pointed out that all preparations of riboflavin deteriorate on exposure to light.

Vitamin B-6 is another of the water-soluble, heat-stabile components of the vitamin B-complex which have been synthesized. It is a derivative of the nitrogenous base, pyridine, which is also the fundamental ring structure in nicotinic acid. (Editorial: Jour. Amer. Med. Assoc.; 1939.) Vitamin B-6 prevents dermatitis in rats, and anaemia in dogs (Bessey: p. 1037). Very recently, the view has been advanced that B-6 is important also for the nutrition of man. Spies, Bean and Ashe (1939 b) reported persistance of muscular weakness, nervousness, insomnia and abdominal pain in four cases of vitamin deficiency. Their patients had been kept on a deficient diet but had been successfully treated specifically for the other symptoms of pellagra and of beriberi. The authors said that "within four hours after the administration of 50 mg. of pure synthetic vitamin B-6 in sterile physiologic solution of sodium chloride, all patients expe-

rienced dramatic relief of these symptoms and increased strength." The drug was "injected," but whether intravenously or otherwise, was not stated.

Pantothenic Acid.—An article by Spies, Stanbery and others (1940) concludes with the statement that their "observations indicate that pantothenic acid is essential to human nutrition and that its function is probably associated with that of riboflavin."

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Chapter XXXV

SCURVY

Synonyms.—Scorbutus, Barlow's Disease (in infants).

Definition.—Scurvy is a disease of the tissues caused by deficiency of vitamin C.

Geographical Distribution.—In the Tropics, scurvy is seldom seen except in laborers who have been removed from their usual environment and fed on diets consisting largely of cereals and canned foods. It has been common in the arctic regions, except among Eskimos who live on their traditional dietary. Sporadic cases may be found in almost any part of the world.

Incidence.—Neither sex, and no age-group is exempt. In the past, scurvy has been common in labor camps in the Tropics, on expeditions to the Arctic, and on sailing ships which remained at sea for long periods of time. Outbreaks of scurvy have repeatedly followed failure of crops. In the United States today and probably in other parts of the temperate zone, scurvy in adults occurs particularly among ill nourished individuals who live alone and who prepare most of their own meals. Under these conditions, the diet is likely to be deficient in fresh fruits and vegetables. Sporadic cases are to be expected in bottle-fed infants who have not been given fruit juices. Diffusion of knowledge about the cause and prevention of scurvy, has greatly reduced the incidence of this disease.

Etiology

Scurvy is caused by deficient ingestion of foods which are rich in vitamin C, or by defective absorption of the vitamin from the intestine. It seems possible that advanced liver disease may interfere with the utilization of vitamin C and thus favor the development of scurvy. The ordinary dietaries of natives of the Tropics and of the Arctic are adequate to protect against scurvy. Vitamin C is readily destroyed by oxidation. When protected against oxidation it can withstand a good deal of heat. Lightly broiled or roasted meat may retain much of this vitamin but boiling is likely to destroy a large proportion of it. Raw fruits and vegetables, particularly when fresh, are rich in vitamin C. Stefansson's observations among the Eskimos prove that meat and fish eaten raw, even when putrid, will prevent scurvy; and that boiled meat has little protective power. He was inclined to believe that common salt, when added to food, favors the development of scurvy. The evidence in support of this hypothesis is scanty. However, meat which has been preserved by means of salt does not protect against scurvy. The amount

of vitamin C retained in canned or preserved food depends on the method of preservation. Some of the canned foods are said to retain nearly, if not all the vitamin C originally present in the food.

Physiology.—Hexuronic acid, isolated some years ago, has since been found to be identical with vitamin C. Since then it has been called cevitamic acid or ascorbic acid and it has been synthesized. Ascorbic acid forms colorless crystals which are soluble in water and in various alcohols. It can be isolated only when protected from oxidation which destroys it.

As Wolbach (1937) has shown, the functions of vitamin C are closely related to maintenance of the integrity of the intercellular substance, to the formation of the bones and of the teeth, and to the maintenance of cartilage and of fibrous tissue in a healthy condition. This vitamin seems also to play an important role in the growth of animals and of plants. The anaemia which may develop in scurvy seems to be caused by dysfunction of the blood-forming tissues.

Man, the other primates, and guinea pigs, cannot synthesize ascorbic acid (King: 1939) but at least some of the other animals can do so. This vitamin is found in high degrees of concentration in the glandular organs and in rapidly growing tissues. Human milk contains four times as much vitamin C as does cow's milk. The quantity in human milk varies markedly with the diet of the mother. A diet inadequate in vitamin C causes marked reduction of this vitamin in the blood plasma and in the amount excreted in the urine. Probably a daily excretion in the urine of 13 mg. of ascorbic acid is close to the lower limit of normal and an output of about 40 mg. indicates that the patient is saturated with vitamin C (Sybil L. Smith 1939). The work of various investigators indicates that the content of reduced ascorbic acid in the fasting blood plasma of normal individuals ranges from a minimum of about 0.6 mg. to a maximum of from 1.5 to 2 mg. or more, per 100 cubic centimeters (S. L. Smith 1939). Friedman et al (1940) who studied the clearance of vitamin C at plasma levels varying from 0.03 to 2.05 mg. per cent, said that their results suggest that the clearance of vitamin C at the low plasma levels is constant.

The need for vitamin C is intimately dependent on the rates of growth and of metabolism. Thus, the infant requires correspondingly larger amounts of the vitamin than does the adult and increased amounts are called for in the presence of fever, infection, or hyperthyroidism.

Pathology

The fundamental pathology of scurvy in man can be reproduced in monkeys or in guinea pigs. The specific lesions have been repeatedly described by Wolbach and his associates. The lesions are characterized by failure of the tissues to produce and to maintain the intercellular substances. These substances are "the collagen of all fibrous tissue structures, the matrices of bone, dentin and cartilage, and all nonepithelial cement substance, including that of the vascular endothelium." (Wolbach: 1937.)

Haemorrhages, large or small, may occur externally or internally. In adults, petechiaes hemorrhages in the hair follicles of the lower legs, large ecchymotic patches on the thighs or trunk, and hematomata in the muscles of the legs are common. Subperiosteal haemorrhages and extravasation of blood around the joints are more frequent in young children. Secondary pyogenic infections are common externally, and infected hematomata may form large abscesses.

Darling, Wolbach, and others have described hypertrophy and dilatation of the heart as features of scurvy in man or in animals. Weiss and Wilkins (1937) have expressed the view, however, that these cardiac changes in man are to be attributed to coincident deficiency of vitamin B-1 rather than to lack of vitamin C. According to Wolbach, calcium metabolism is not primarily disturbed but calcium is deposited in a characteristic manner at the epidiaphyseal junctions and in cartilage of joints. In advanced scurvy, the absorption of calcium from the bones leads to osteoporosis. Through resorption of the alveolar processes of the teeth and weakening of supporting structures, the teeth become loose. In growing teeth, the formation of dentin ceases. Swelling of the gums and haemorrhages from them are common.

In advanced cases, anaemia may become pronounced. Oedema of the ankles is usually present. It may involve the face or even become generalized. Effusion into serous cavities and particularly into the pericardium are common.

Symptomatology

The clinical picture of scurvy has been described in detail by Hess (1920). The earliest recognizable symptoms are increasing weakness, lethargy, irritability, and dizziness. The appetite is lost and an inordinate craving for salt may develop. In more advanced cases, petechial haemorrhages appear around the hair follicles on the lower legs, or large ecchymotic patches may be seen on the thighs or on other parts of the body. Swellings, which may reach considerable size, are caused by extravasation of blood into the larger muscles. Over these swellings there are patches of oedema. The affected muscles ache, they are acutely sensitive to pressure, and use of the limbs increases the pain. Lesions of the eye, the brain, or the cord may result from haemorrhage into these structures. Recent studies by Alexander and Putnam (1937) of Wernicke's paralysis, point to deficiency of vitamin B-1 as the cause of the minute, haemorrhagic cranial lesions which characterize this disease.

Oedema of the ankles or of the lower legs is usually present. The face may become bloated, and effusion into the pericardium or other serous cavities may develop.

External pyogenic infections, such as hordeolum, or boils, are common, and ulcers may develop on the legs. Large abscesses may result from infection of haematomata. The edges of the gums, except in edentulous persons, are denuded and reddened. Later, the gums become swollen, bluish and "spongy." Fungating projections from the ulcerated surfaces

partly cover the teeth. Secondary infection gives the appearance of advanced pyorrhea, the breath becomes foul, and the teeth become loose in their sockets. Loss of blood from epistaxis, haematuria, haematemesis or even from the tooth-sockets may be considerable. Capillary oozing may be uncontrollable. The white count may fall gradually, but the differential count is little changed.

Usually there is anaemia. It may be caused by reduced activity of the blood-forming organs or by loss of blood. Anaemia occurs less often in children than in adults. In the latter, it may be extreme. The complexion becomes sallow and muddy in appearance through increased pigmentation of the skin. The tongue swells and the salivary and the lymphatic glands increase in size.

Dyspnoea on exertion, cyanosis of the lips, tachycardia and pulmonary congestion may develop. Slight exertion is often followed by sudden cardiac death even when the patient appeared comfortable while at rest. One may suspect that these cardiac symptoms are due to coincident deficiency of vitamin B-1 rather than to lack of vitamin C (p. 1041).

In young children, ecchymoses, petechial haemorrhages, and haematomata in the muscles are seldom seen but haemorrhages about the joints and under the periosteum of the long bones are usually demonstrable. Swelling in the epiphyseal region at the wrist and nodular enlargements at the costochondral junctions, which resemble the rachitic rosary, are to be expected. In advanced cases, separation of the epiphysis may occur.

The skin becomes dry and rough in scurvy. When the hand is passed lightly over the legs of the patient, the papillary keratosis around the hair follicles is easily felt. Scurvy may account for delayed healing of a wound, for the breaking down of an ulcer, or for failure of a fracture to unite or may even be the cause of a fracture.

Vitamin C deficiency, when it develops naturally in man, is often associated with more or less deficiency of various other essential food factors. Ship beriberi and Rand scurvy are combined deficiency diseases which show the symptoms of scurvy and of beriberi. Night blindness, formerly regarded as an occasional symptom of scurvy, is known now to be caused, as a rule, by deficiency of vitamin A. The keratosis seen in scurvy is not readily distinguishable from that of vitamin A deficiency.

Diagnosis

In well marked cases of scurvy, diagnosis is easy. Nevertheless, this disease has often been overlooked through failure to consider it as among the possibilities. Thrombocytopenic purpura, leukaemia, and mercurial poisoning may produce lesions of the gums suggestive of scurvy. It should be possible to diagnose these conditions by positive evidence. On the other hand, lead is said to combine so freely with ascorbic acid in the body that excess of lead may induce scurvy unless a large amount of the acid is taken. In cases of pyorrhoea alveolaris or of "trench mouth," the dietary history should be carefully investigated and, if scurvy seems a possible diagnosis, appropriate treatment should be instituted.

The response to treatment with vitamin C, in cases of scurvy, is so rapid as to be of great diagnostic value in doubtful cases. Low levels of urinary excretion and of blood plasma values for vitamin C seem to indicate deficiency of vitamin C. These findings occur frequently, however, without other demonstrable evidence of scurvy and are of limited diagnostic significance. Capillary resistance tests are usually positive in scurvy and they may be positive in the prescorbutic stage of vitamin C deficiency. They have been reported as positive also in a notable proportion of apparently healthy and well nourished children whose diets were believed to be adequate in vitamin C. For this reason and because increased capillary fragility occurs in a number of conditions aside from scurvy, the diagnostic value of the capillary resistance test is small (Greene: 1934).

Anaemia may be so pronounced as to mislead the clinician who is not familiar with this manifestation of scurvy. Erroneous diagnoses of rheumatic pain, myositis, or neurasthenia may be made in the earlier stages of scurvy.

In children, roentgenologic examination of growing bones reveals characteristic lesions at the junction of the shaft and the epiphysis and often subperiosteal haemorrhages as well. Characteristic lesions at the costochondral junctions may be found in adults or in children.

A test of the blood plasma concentration of ascorbic acid at a given time or of the twenty-four hour excretion of this substance in the urine is of limited value for diagnosis. Saturation tests, for which large amounts of ascorbic acid are administered and the excretion in the urine determined quantitatively for a definite period, are more significant. No standard method has yet received general acceptance. The methods used were discussed by Sybil L. Smith (1939) and some of them were tested by Crandon, Lund and Dill (1940).

Prognosis is excellent in uncomplicated cases provided that treatment be begun in time and that the patient be kept at rest until convalescence is well established. In untreated cases, death results from exhaustion, cardiac failure, or intercurrent infection. In young children, bronchopneumonia is apt to be the immediate cause of death.

PROPHYLAXIS

The main points in the prevention of scurvy follow directly upon what is known of etiology and treatment. Neither the optimal nor the minimal daily requirement of vitamin C has been determined with certainty. As a result of their experiments on three adult males, Ralli and associates (1939) have stated that a blood plasma concentration of 1.0 mgm. per cent can only be obtained and maintained on a daily intake of at least 100 mg. of vitamin C. They suggested that this be considered the optimum intake.

Sybil L. Smith (1938) said that "The estimated requirements for various age groups as reviewed lie within the following limits of absolute values: Infants, from about 8 mg. (newly born) to 50 mg. daily; children,

from 22 to 100 mg. or more; adults, from 28 to 100 mg. or more. With due allowance for unlike methods followed in their determination, these values may be considered to represent roughly the range from the physiologically indispensable minimum to saturation or luxus consumption. Values of about 20 mg. daily for infants, 40 mg. for children and from 50 to 60 mg. for adults may be considered as tentative estimates for the middle or barely adequate consumption level, with but little margin of safety or allowance for individual variations in requirement."

Growth, pregnancy, lactation, and other conditions which elevate the metabolic rate, increase the requirement of the body for vitamin C. According to Chandler (1939), recent estimates of the vitamin C requirement for a pregnant woman run from 75 to 125 mgm. and, for a nursing woman, from 100 to 150 mgm. per day.

There are indications that the requirement for vitamin C is increased by diarrhoea, in tuberculosis, in certain cases of liver disease, after surgical operations, and by the ingestion of excessive amounts of lead. Ascorbic acid combines readily with lead so that painters tend to develop scurvy. On the other hand, by taking large amounts of vitamin C they can, to some extent, protect themselves from lead poisoning (Chandler: 1939).

Treatment

As a rule, all the symptoms of scurvy respond promptly to adequate dietary treatment. Much relief is to be expected within from two days to a week. Therefore, it is seldom necessary to administer vitamin C in pure form. The diet should supply not less than 300 mg. of ascorbic acid, an amount which is contained in a pint of fresh orange juice.

Little positive information is available about the absorption and storage of vitamin C. It is believed, however, that absorption takes place chiefly in the small intestine, and there is evidence indicating that absorption is occasionally defective. Therefore, should a patient fail to respond to the usual dietary treatment, it may be necessary greatly to increase the vitamin C content of the diet or to administer with it a pure preparation of ascorbic acid in considerable amounts.

Ascorbic acid can be administered in tablet form by mouth, intramuscularly or intravenously. Ascorbic acid should be administered by one of these methods when adequate amounts of vitamin C cannot be ingested in the form of food.

According to New and Nonofficial Remedies (1939), 10 mg. of pure ascorbic acid daily is a protective dose for an infant. The therapeutic dose is 30 to 50 mg. daily, but the requirement in certain cases may be considerably higher. Sodium ascorbate is recommended for parenteral injection in concentrated form when vomiting, diarrhea, or other conditions prevent utilization of the vitamin by mouth in adequate amounts (New and Nonofficial Remedies: 1939).

Repeated doses of as much as 1 to 6 Gm. of crystalline vitamin C have been administered orally or intravenously to adults without producing toxic effects (Abt and Farmer: 1939).

Sources of Vitamin C

General information about the occurrence of vitamin C in food has been given already (p. 1074). The short list which follows shows the usual vitamin C content of a few common foods.

Approximate Ascorbic Acid Values in Milligrams per Ounce of Food and per Pint of Milk*

	Mg.
Citrus fruit juice	18 to 20
Tomatoes or tomato juice	8 to 10
Greens properly cooked	5 to 10
Raw green peppers	50
Fresh raw vegetables	5 to 10
Cooked fresh or canned vegetables	2 to 5
Potatoes, properly cooked	3 to 5
Pineapple and strawberries, fresh	8
Pineapple, canned or juice	3
Apples and most other fruits	0.5 to 3.5
Pasteurized milk, per pint	3 to 6

Among the richest food sources of vitamin C are oranges, lemons, grape-fruit (raw or canned), tomatoes (raw or canned), green peppers, raw cabbage, and other green, leafy vegetables. Dry cereals and legumes are devoid of vitamin C, but almost any kind of seed, if kept moist until it sprouts, will become an effective antiscorbutic. The vitamin C content of fruits increases as they approach maturity, but pears and green corn show a higher content of this vitamin during the tender stage. Certain varieties of the same kind of fruits and vegetables are richer in vitamin C than are other varieties.

According to Abt and Farmer (1939), canned tomato juice and the canned juices of citrus fruits are rich in vitamin C.

Storage and Preservation.—Time and warm temperatures have deleterious effects on vitamin C. Wilted spinach, for example, has lost about half of its vitamin values. Potatoes and other root crops lose the vitamin but slowly under usual conditions.

Although quick freezing is believed to have little effect on the vitamin C value of fruits and vegetables, shelling, washing and blanching are said to reduce it materially and traces of copper salts, which are used for spraying fruit and vegetables, will quickly destroy the vitamin.

Drying, *per se*, does not destroy vitamin C but oxidation usually does so during the process of drying. Dehydrates foods are usually devoid of vitamin C for the same reason. Pickling, salting, "curing," or fermenting usually eliminates vitamin C.

Cooking and Canning.—Contact with copper vessels, access of air, prolonged heating and alkalinity are to be avoided in cooking or canning. An acid medium tends to conserve vitamin C.

* *Vitamins in Human Nutrition. A. C. Chandler. The Rice Institute Pamphlet; vol.* 26; 1939.

When crushed or shredded in the raw state, vegetables such as spinach, cabbage, or turnips lose much of their vitamin C through liberation of enzymes. It is well to start the cooking of vegetables in hot water because these enzymes are then quickly destroyed. The addition of soda to the tooking water tends to destroy vitamin C.

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SECTION V

DISEASES NOT SATISFACTORILY GROUPED IN OTHER SECTIONS

Chapter XXXVI

ACUTE EFFECTS OF HEAT

General Information

Classification.—Acute effects of heat in man are manifested by reactions which may be mild or severe. Any classification of the clinical types of response to heat is necessarily arbitrary because of the existence of numerous borderline cases. Three principal categories of cases, based upon outstanding symptoms, and differing in their mechanism of production, are commonly recognized; namely, *heat exhaustion*, in which prostration is associated with a body temperature which is subnormal, normal, or but little elevated; *heat pyrexia*, in which the temperature is considerably or extremely elevated; and *heat cramps*, in which cramps in the muscles dominate the picture.

Because nomenclature is chaotic and criteria for diagnosis differ, and because cases of borderline character are numerous, reliable data on the relative frequency of the various clinical types of response are not available.

Physiological Responses to Heat.—In general, exposure to heat causes increase in the rate of the pulse and of the respiration and a consequent diminution of ability to perform muscular work. Sweating is usually profuse, but cessation of sweating may precede the onset of high fever. The cause of this cessation has not yet been determined. Some authors believe and others deny that dehydration of the body or marked depletion of sodium chloride in the blood are causative. It is generally conceded, however, that adequate ingestion of fluid favors sweating and it has been demonstrated that heat cramps can be prevented or cured by administration of ample quantities of sodium chloride. The sodium and the chloride in the blood can become depleted as a result of prolonged and profuse sweating, repeated vomiting or persistent diarrhoea. Dehydration can result from the same causes, or from inadequate ingestion of water. The carbon dioxide combining power of the blood may be reduced by exposure to heat. There is pronounced disagreement among observers

as to the occurrence of many of the other metabolic disturbances which have been reported in cases of heat pyrexia.

Heat loss in man occurs through conduction, convection, radiation, or vaporization at atmospheric temperatures below that of the body. At higher atmospheric temperatures, vaporization of sweat becomes the chief means of dissipating excess of heat. Air movement over the skin favors dissipation of heat but high atmospheric humidity interferes with heat loss by vaporization.

Adaptation or Acclimatization.—Constant or frequently repeated exposure to heat brings about increase in the power to sweat and a reduced excretion of sodium chloride in the sweat. These changes can develop within a period of two weeks or less. They may disappear in an even shorter time after cessation of the exposure to heat.

Geographical Distribution.—According to the experience of Castellani and Chalmers (1919), heat pyrexia ("heat stroke") is the usual form of response to excessive heat in the tropics. They have called attention to the special prevalence of heat pyrexia in certain parts of India, including the Northwest Provinces, and to its comparative scarcity in Ceylon. Biggam (1942) in the disembarkation of troops in the Red Sea observed 40 cases among which there were 8 deaths.

Cases of heat pyrexia were very numerous twenty years or more ago in the British Army in India, and also among the British and French soldiers in other colonial possessions in the tropics. Regulations since promulgated in India have greatly reduced the incidence of these cases. French statistics, examined a few years ago (Shattuck and Hilferty: 1936), showed that for many years there have been few deaths from heat in the French colonial possessions. It was found also that deaths attributed to heat were notably common in the United States, in Australia, and in India. Figures obtained from Central America, South America, Africa and Asia were inadequate as a basis for sound generalization. Naval and marine personnel on shipboard in the tropics and stokers, particularly, are frequently attacked by heat pyrexia or overcome by heat exhaustion.

In the United States, deaths from the effects of heat were far more common in urban than in rural communities. They were especially numerous in the larger cities of the Northern States, where they occurred chiefly in July and August during heat-waves of several days duration.

Until the means of preventing them became known, heat cramps were common in the United States and elsewhere among men doing hard physical labor while exposed to great heat. Cases of heat cramps occur occasionally in the tropics and elsewhere in association with heat pyrexia.

Prophylaxis

Susceptibility.—The power of individuals to become acclimatized to heat differs. In general, bodily vigor and adaptability of the circulatory system reduces susceptibility. Persons who have organic disease of the heart or kidneys, of a character which seriously impairs the function of these organs, should be advised not to go to the tropics. Similar advice should be given to persons who have hyperthyroidism or ichthyosis or whose power to sweat is defective.

Individuals who have been living in a temperate environment should be especially cautious, at first, about exposing themselves to great heat in the tropics or elsewhere. Important physiological adjustments usually take place within a period of about two weeks or less after the beginning of exposure to unusual heat.

There are indications that natives of the British Isles are more susceptible to heat than are other races. According to Stott (1936), Indian troops in Mesopotamia very rarely showed acute heat effects. In 50 per cent of such cases, malaria was considered to be the exciting cause.

Housing.—In hot climates, buildings should be designed to protect against the sun and to provide for good ventilation and free air movement. A double roof, having a well ventilated air space, is useful. A tent pitched in the sun should always have a fly above it. A thatched roof is cool, but corrugated iron becomes very hot when exposed to the sun, and heat penetrates it freely. Trees and vegetation around a dwelling not only provide shade and reduce reflected light, but they cool the atmosphere by promoting the evaporation of moisture. Massive walls absorb heat slowly. Venetian blinds, awnings, punkas and electric fans are useful adjuncts.

Hours of work should begin early. Either they should end at noon or work should be discontinued between noon and three or four o'clock in the afternoon. Physical exertion in particular should be avoided, whenever possible, during the hotter hours of the day. The tempo of work should be less than in temperate climates and great fatigue is to be avoided.

Exercise and Rest.—Sedentary workers benefit greatly by regular exercise taken during the cooler hours of the early morning or late afternoon. A rest period during the hours of greatest heat is to be recommended.

Food and Drink.—The ordinary rules of hygiene should be more scrupulously followed in the tropics than in the temperate zone.

As to diet, it may be desirable to restrict starches and sugars which are heat producers but proteins may be eaten freely. Alcoholic beverages are strictly to be avoided until after sundown. Water and common salt should be taken much more freely than is necessary in cool weather. (See Heat Cramps.)

The Division of Occupational Hygiene of the Department of Labor and Industries of The Commonwealth of Massachusetts (Leaflet No. 154; July, 1939) recommended that, with the beginning of hot weather, salt should be applied liberally to food at the table and added to drinks such as tomato juice. Approximately 2 teaspoonfuls of salt should be taken daily in hot weather by workmen and by all persons who perspire freely. Those doing sedentary work may require only 1 teaspoonful in addition to that contained in the diet. Like precautions might well be taken by recent arrivals in the tropics.

Clothing.—In parts of the tropics where heat is continuous and where the fluctuations of temperature are not pronounced, the nearly naked savage exemplifies the ideal in clothing. Clothing should be of very

light, porous material which will absorb perspiration and favor its evaporation by admitting air. "Shorts" and short sleeved shirts, open at the neck and worn without a tie, are to be recommended for coolness. All clothing should be loose. If worn in the sun, it should be white or of very light color. Starched clothing is relatively impervious to air and, therefore, does not fulfill the requirements. The waistcoat should be taboo, and it is well to dispense with the coat when circumstances permit. The need for protection against insects or against rapid changes of temperature which occur in some parts of the tropics may modify the clothing requirements.

Some Europeans have been able without injury to expose their heads repeatedly and for hours at a time to the direct rays of a tropical sun. Nevertheless, use of the helmet, which shades the eyes and the nape of the neck, and which by its detached head-band permits circulation of air around the crown of the head, can confidently be recommended as the best type of headgear for protection against the sun's rays. It is well to wear the helmet even when the sun is obscured because some of the heat rays may have considerable power to penetrate clouds. Helmets are seldom worn in the islands of the Pacific or in the American tropics, but umbrellas are often carried in the Philippine Islands. The sun is feared far less in these localities than in India or in the British and French possessions in Africa and in the Far East. The reason for these marked differences of experience and of custom are by no means clear.

Air-conditioning, if not carried too far, undoubtedly has value for the prevention of acute heat effects. The best methods of using it for the purpose have not yet been definitely established.

Heat Pyrexia

Synonyms.—Thermic Fever. Heat Hyperpyrexia. Heat Stroke. Sun Stroke. Sun Traumatism. Siriasis.

Definition.—Heat pyrexia is a condition characterized, in severe cases, by high fever and associated symptoms which have been caused by exposure to excessive heat. Circulatory collapse and coma may develop in the advanced stages.

Incidence.—All ages, both sexes, and all races so far as is known, are subject to heat pyrexia. Men are more frequently attacked than are women. The highest death rates occur among infants and elderly persons, and the lowest among children and young persons. Where death rates of men of working age are relatively high, they are influenced by occupational factors. Urban death rates are constantly high as compared with those for rural areas.

In the southern United States, deaths from heat pyrexia are more common among Negroes than among Whites (Shattuck and Hilferty: 1932). This can be attributed to the fact that, in the South, the Negro does most of the heavy manual labor. In the large northern cities of the United States, heat pyrexia is a common cause of death after a series of unusually hot days in July or August.

Although proof is lacking, there are indications that natives of the British Isles are more liable to heat pyrexia in the tropics than are members of other races of western Europe. Recent arrivals in the tropics in particular, are subject to this disorder.

ETIOLOGY

When the cooling mechanisms of the body fail to dissipate excess of heat which is generated from within or acquired from without, the temperature of the body rises. Heat pyrexia commonly develops after prolonged exposure to excessive environmental air temperatures. Other atmospherical conditions which may contribute to its causation are high relative humidity and absence of air movement. Cessation of perspiration has often been observed in advance of an attack of heat pyrexia. The cause of this phenomenon is by no means clear. It is known, however, that ingestion of adequate amounts of water favors perspiration and that the power of individuals to perspire freely varies greatly.

Among important factors which may be operative in the production of heat pyrexia are strenuous physical exertion, heavy or tight clothing which does not allow free access of air to the skin, ill-ventilated housing, the ingestion of alcoholic beverages, the lack of physiological adaptation to heat, and debilitating diseases.

It is no longer believed that the ultra-violet rays of the sun are important in the causation of heat pyrexia, but that the longer heat rays, which have greater penetrating power, are significant.

Some of the prodromal symptoms, such as headache, nervous irritability, and intolerance of light can undoubtedly be aggravated or even induced by exposure of the eyes to brilliant sunlight, whether direct or reflected.

The mechanism of the circulatory disorders caused by high body temperatures induced by exposure to heat has not been adequately explained. On the basis of animal experiments, however, Dérobert (1939) reached the conclusion that the essential phenomena of heat-stroke are to be accounted for by the disintegration of protein. He regarded the heat-stroke syndrome as closely related to anaphylactic and protein shock.

PATHOLOGY

Body temperature may continue to rise after death. *Rigor mortis* sets in early. Decomposition proceeds rapidly. The blood shows little tendency to coagulate and the blood and tissues may show increased acidity. The organs in general are congested. The left ventricle of the heart is often firmly contracted but the right ventricle may be dilated. Engorgement of the lungs is sometimes so marked as to render them almost black. E. E. Smith (1928) said there is interstitial pneumonitis. Occasionally, the mucosa of the stomach and of the intestines is swollen. Minute haemorrhages may be found in the skin, the internal organs and the brain. Signs of congestion occur in the vessels of the meninges, the brain and the medulla. Wilson (1940), in addition to petechiae in the

central nervous system, found in 4 of his cases a fairly extensive haemorrhage of the ventricular septum in the region of the bundle of His. Intracerebral and spinal fluid is apt to be increased in amount. Coagulative necrosis of cells has been observed in some of the cells of the central nervous system. Cloudy swelling may occur in the myocardium, the liver, and the kidneys. Enlargement of the spleen, when present, appears to be attributable to causes other than heat.

SYMPTOMATOLOGY

Cessation of sweating may occur as much as 48 hours in advance of the attack. Mild prodromal disorders, such as listlessness, muscular weakness, headache, vertigo, anorexia, pronounced thirst and slight increase of body temperature and of pulse rate, usually precede the onset of high fever but further development of symptoms may not occur.

Among other symptoms which have been observed are suffusion of the eyes, photophobia, chromatopsia, irritability of the bladder. Scantiness of the urine may occur. Probably, it is an indication of dehydration. Some authors assert that urine is usually passed in considerable amounts. Nausea or vomiting, precordial distress, a sense of impending calamity, muscular twitching, and manifestations simulating hysteria have also been recorded. There may be a short period of restlessness or of irritability and unreasonableness.

A sharp rise of body temperature to 105°F., 110°F. or even higher, supervenes suddenly. It may be accompanied by delirium and it is followed by cyanosis and somnolence deepening into coma. There may be more or less muscular rigidity. Convulsions or vomiting are common concomitant symptoms of grave import. A person attacked during the night may be found dead in the morning.

Irregularity of the breathing or the Cheyne-Stokes type of respiration are grave symptoms. The pupils are contracted until the terminal stages, when they become dilated. The knee jerks and pupillary reflexes are usually diminished or abolished. The pulse, at first rapid, full and regular, and of increased tension, becomes small, feeble, and irregular. Cyanosis and "clamminess" of the skin appear as late symptoms. Death has been variously attributed to stopping of the heart and to failure of the respiration.

During the attack, the urine generally contains albumen and the chlorides are markedly reduced. The spinal fluid is clear but the pressure is usually increased. Constipation is the rule, but heat pyrexia may be associated with profuse vomiting or with cholera-like diarrhoea. Heat cramps develop in some of these cases through depletion of sodium chloride. Very profuse sweating may have similar effects.

In cases which recover, the temperature falls rapidly, diuresis occurs, the pulse improves and the patient sleeps. Resumption of sweating is a favorable sign. The fever and other symptoms may recur within a few hours after successful treatment of the primary attack. There may even be several such relapses.

COMPLICATIONS AND SEQUELAE

Owing to the pulmonary congestion incidental to heat pyrexia, bronchopneumonia is a common and dangerous sequel. The power to sweat may remain in abeyance for three weeks or longer after an attack of heat pyrexia and the knee jerks may not return for some time. These phenomena are indications for continued caution.

When moderate fever persists for some days, intercurrent infection is to be suspected. Headache, photophobia, and giddiness may continue for a week or more. Cerebral or cerebellar symptoms are among the serious sequelae. Usually, they disappear gradually. It has been commonly observed that persons who have suffered even mildly from the effects of heat may remain abnormally susceptible to it for many years thereafter.

DIAGNOSIS

Circumstances give presumptive indications of the nature of the malady. An attack of pernicious malaria may simulate heat pyrexia or vice-versa. The finding of malarial parasites in the blood indicates that malaria may be an important factor, although not necessarily the sole cause of symptoms. Failure to find parasites in the peripheral blood, however, does not exclude subtertian malaria. Splenic enlargement, when present, is likely to be of malarial origin. The hot, dry skin and high fever differentiate heat pyrexia from heat exhaustion. Meningitis, enteric fevers, and pneumonia should not be overlooked. Uraemia and apoplexy are usually afebrile.

Prognosis depends on the degree of severity of the symptoms, the promptness and efficacy of the treatment, the age of the patient, his vitality, and the presence or absence of complicating conditions. Cardiac or renal disease, acute or chronic alcoholism, or preexisting debility from any cause, militate seriously against recovery. Percentage mortality rates are dependent upon many variables. In hospitalized cases, they range from about 15 to about 50 per cent. The prognosis is excellent in mild cases in which high fever does not develop.

TREATMENT

When there is high fever, the essentials of treatment are rest, rapid reduction of temperature, replacement of lost fluid, cardiac or circulatory stimulation as indicated by the symptoms and, sometimes, control of convulsions. The patient should be placed at once in a recumbent position in the coolest available place. Free circulation of fresh air is important. The clothing should be removed.

To reduce temperature, rubbing with ice and colonic injections of ice-water have been recommended but these procedures may be too drastic. Sponging with cold water accompanied by vigorous friction applied to the skin, wrapping the patient in a wet sheet which is sprayed with water at

intervals while air movement is maintained by fanning, are alternative methods of reducing temperature. Meanwhile, the patient's temperature should be taken at intervals of every few minutes. Rectal readings are best except when colonic irrigations are being used. False thermometer readings caused by high atmospheric temperatures are to be guarded against. During treatment the patient's temperature usually falls rapidly and it continues to fall for a time after the cooling procedures have been discontinued. To prevent the temperature from reaching subnormal levels, the cooling treatment should be stopped promptly when the patient's temperature has fallen to 102° or 103°F. The patient should then be wrapped in a light, dry blanket.

Lest high fever supervene, mild cases should be treated promptly by rest in a cool and airy place, cool baths, and free ingestion of fluid. The patient's condition should be closely watched until the symptoms have abated.

According to Marsh (1930), excellent results in the treatment of heat cases have been obtained by the Anglo-Persian Oil Company which operates in South Persia. In their hospitals, cases of heat pyrexia are treated in special wards in which the temperature is kept at 65°F. and the humidity is maintained at a low level. All cases of fever occurring in outlying stations are placed, during the heat of the day, in a cold-storage chamber attached to the local ice-plant. During the coolest part of the night, they are quickly transferred by ambulance to the nearest hospital.

The mechanism of the circulatory disorders of heat pyrexia is not well understood. Quickly acting cardiac stimulants such as aromatic spirits of ammonia and injections of camphor or of strophanthin are believed to be valuable when pulmonary congestion or other signs of cardiac embarrassment exist. When there is cyanosis, venous engorgement and marked pulmonary congestion, venesection may be beneficial. Caffeine may be helpful as a circulatory stimulant. Although frequently recommended in the past, strychnine is probably of no value as a circulatory stimulant.

Dehydration may well be an important factor in the causation of some of the circulatory disorders which develop with heat pyrexia. In any case, fluid should be administered freely to promote sweating while the cooling treatment is being carried out. Intravenous injections of normal salt solution or of salt solution and 5 per cent dextrose have been followed by highly beneficial results. Free administration of salt solution is required when muscular cramps are present. It has not been demonstrated that dextrose is of definite value in cases of heat pyrexia or of heat cramps.

Light chloroform anaesthesia is frequently employed to control convulsions. Morphine has been used for this purpose but not always with success. When the cerebrospinal fluid pressure is increased, withdrawal of fluid by lumbar puncture may be desirable.

If the presence of malaria has been demonstrated or even suspected, injections of a suitable quinine salt in adequate dosage is imperative.

Prophylaxis.—The precautions to be recommended in general have been outlined on page 1083.

By preliminary exposures of new mine workers to greater degrees of heat than those to be encountered by them under working conditions, Dreosti believed that some degree of acclimatization and resistance to the ill effects of heat could be induced (Dérobert: 1939).

Heat Exhaustion

Synonyms.—Heat Prostration. Heat Syncope.

Definition.—Heat exhaustion is a certain type of response to exposure to excessive heat. The condition is characterized by prostration and concomitant circulatory disorders which are associated with little if any rise of body temperature.

ETIOLOGY

The climatic causes of heat exhaustion are the same as those of heat pyrexia. Under identical external conditions, heat exhaustion may develop in one individual and heat pyrexia in another. Probably the type of response to heat is determined by physical condition, fatigue, alcoholism, or the existence of intercurrent disease. Chronic circulatory disorders, debilitating diseases, the ravages of age, and fatigue resulting from unaccustomed physical exertion, predispose to heat exhaustion.

PATHOLOGY

The pathology of heat exhaustion is not characteristic. The lesions are those consequent upon circulatory failure.

SYMPTOMATOLOGY

Symptoms usually develop rapidly, sometimes suddenly. Among them are weakness, nausea, headache, giddiness, and staggering. In attempting to walk, the patient may fall and he may even lose consciousness. There may be an initial rise of temperature to 100° or 102°F. More often the temperature is normal or subnormal. A sickly pallor, a low blood pressure with a small, weak and rapid pulse, dilated pupils, and a moist "clammy" skin are the rule.

Mild cases recover rather promptly under rest alone, but deaths due to circulatory collapse are not uncommon. The nature of the circulatory disturbances appears to be variable, but the picture more often resembles that of shock than of cardiac decompensation.

Diagnosis may require exclusion of acute alcoholism, uraemia, apoplexy, epilepsy and opium poisoning.

Prognosis is favorable except in the presence of serious intercurrent disease and particularly when there is significant pathology of the circulatory system or of the kidneys. Heat exhaustion is often reported as a secondary cause of death in the elderly and in persons debilitated by disease or recovering from operative procedures.

TREATMENT

In general, rest and supportive treatment are required. Clothing which might impede the circulation should be loosened. The patient should lie quietly in a shady place where there is free circulation of air. Strong drafts are to be avoided.

If the body temperature is subnormal, the patient should be wrapped loosely in blankets, and hot water bottles should be applied to the feet. Hot tea, aromatic spirits of ammonia, or whiskey may help to relieve the patient. A hypodermic injection of caffeine or of a preparation of digitalis may be required. Although frequently recommended, strychnine is useless.

PROPHYLAXIS

The general indications have been outlined on page 1083. McCord and Ferenbaugh (1931) believed that pathological fatigue or exhaustion in soldiers, following upon physical exertion under unfavorable conditions of heat and humidity, can be caused by excessive loss of water and of chloride through sweating. For the prevention and control of pathological fatigue, they recommended the use of salinized drinking water 0.25 to 1.0 per cent.

Heat Cramps

Synonyms.—Miner's Cramps. Stoker's Cramps. Cane Cutter's Cramps. Firemen's Cramps.

Definition.—Painful spasms of the voluntary musculature following muscular activity in a high environmental temperature (Talbott: 1935).

Incidence.—Data on the distribution and prevalence of heat cramps are scanty. Talbott (1935) said that the incidence of heat cramps is high in industries in which large numbers of men do hard muscular work in high climatic or environmental working temperatures. When hot weather succeeds a period of cool weather, cases of heat cramps among workmen begin to appear promptly; whereas cases of heat exhaustion succeed after several days of heat.

ETIOLOGY

Cases of heat cramps occurring in the steel industry in Ohio develop chiefly in the summer months. Thus, the incidence of these cases depends in part on high environmental temperatures incidental to certain kinds of labor and in part on the high climatic temperatures of seasonal origin. Heat cramps may be common where the relative humidity is high or low. Relative humidity therefore is of secondary importance as compared with temperature.

Deficiency of sodium and of chloride appears to be the essential cause of heat cramps. Much sodium chloride passes out in the sweat of persons who have not become adapted (acclimatized) to hard labor at high tem-

peratures. On the other hand, after adaptation has occurred, the percentage of sodium chloride in the sweat is comparatively low. Deficiency of sodium chloride may be brought about or aggravated through loss of this substance by vomiting or diarrhoea, or by inadequate ingestion of the salt. Among conditions predisposing to heat cramps are lack of appetite, ill health, unhygienic living, and acute alcoholism.

Exposure to heat causes at first a dilution and then a concentration of the blood. At the stage at which heat cramps appear, there is apt to be an increased concentration of serum protein (globulin), resulting from anhydremia of the blood. All of the electrolytes in the blood serum except the bicarbonate ion may show variations from the normal, but decrease of sodium and of chloride alone seems to bear a significant relationship to the symptoms (Talbott: 1935).

PATHOLOGY

Little is known of the pathology of uncomplicated cases of heat cramps, because deaths are few. In some of the fatal cases, the heat cramps have been associated with heat pyrexia, a condition which is a frequent cause of death (Smith: 1928).

SYMPTOMATOLOGY

Heat cramps are usually manifested in the muscles of the extremities. The cramps may be so slight as to involve only a few small muscles or they may occur in most of the skeletal muscles. They are transitory and they tend to recur at longer or shorter intervals in proportion to their severity. When cramps are slight, a man may be able to continue his work. In cases of moderate severity, the condition is disabling and, in severe cases, the pain is excruciating.

The distribution of the cramps is, usually, symmetrical. They are manifested especially in the muscles which men use most in the work. Generally the onset is gradual. Slight spasms are succeeded by cramps which increase in severity until after recovery has begun. It is doubtful whether heat cramps ever involve the smooth muscles of the abdominal viscera or the heart muscle. Smith (1928) believed that they can and Talbott (1935) that they do not occur in these tissues.

Marked increase in pulse rate, respiration rate or temperature, and alteration in the deep reflexes or in the papillary reactions are not symptomatic of heat cramps. When present, these symptoms are attributable to other causes. Constipation is the rule. Vomiting occurs occasionally and diarrhoea occurs rarely.

DIAGNOSIS

Evidence of exposure to unusual heat combined with muscular exertion, employment in an industry which involves hard labor and exposure to heat, or a history of previous attacks in persons so exposed, may point to a diagnosis of heat cramps. The physical examination is essentially negative.

"Nocturnal cramps" in the limbs, when not related to exposure to heat, gastric crisis, and colic of digestive origin, are to be differentiated from heat cramps.

After the cramps have ceased, it may be possible to confirm a diagnosis of heat cramps by reproducing them in the affected muscles. Direct pressure upon these muscles is less reliable for reproducing cramps than is counter pressure applied to a flexed limb. Among other methods of inducing cramps are the application of cold water or exposure to cold air.

Prognosis.—Death is rare in the absence of serious organic disease or of heat pyrexia. The rapidity of spontaneous recovery during rest depends upon the severity of the symptoms. Severe cramps recur for many hours unless checked by appropriate treatment.

TREATMENT

Treatment requires rest, restoration of the sodium and chloride content of the blood serum to the normal level, and correction of anhydremia by replacement of body fluid. Intravenous injections of normal salt solution serve both purposes. Administration of sodium bicarbonate or of dextrose in normal salt solution has been advised. Talbott (1935) doubted their value on the ground that the benefits might have been caused by the salt solution alone. He administered 600 to 1000 cubic centimeters of salt solution by the intravenous route during the first six hours and repeated it if the patient were markedly hydremic. Relief from cramps occurred in all of his cases before the end of the initial infusion. The intravenous route was considered the method of choice until the patient was able to take salt by mouth.

Salt can be given by mouth as milk, as normal salt solution, or in the form of tablets. The dose recommended for the latter was one tablet of 1 Gm. (15 gr.) every hour during the daytime, until 15 tablets had been taken.

A liberal intake of fluid in amount sufficient to compensate for losses by sweating or otherwise is beneficial but of less importance than is replacement of salt.

PROPHYLAXIS

Maintenance of good health is important as a preventive. Adequate rest and a wholesome, nutritious diet are means to this end.

The best method of preventing heat cramps in workmen is to provide them with an abundant supply of drinking water containing sodium chloride. Bock (quoted by Talbott) recommended a concentration of 0.1 to 0.15 per cent in the drinking water. He said that when taken cool, such water had no perceptible saline taste and that it alleviated thirst. McCord and Ferenbaugh (1931) found that stronger solutions tended to increase thirst.

Talbott (1935) estimated that an average ingestion of 15 Grams (225 gr.) of sodium chloride daily is probably necessary for men engaged in hard labor in hot weather. It has long been a custom for coal miners

in England to add salt to their beer and it is said that those who drink salted beer do not suffer from heat cramps. Stokers on vessels sometimes take sea-water for the same purpose.

Men who are newly engaged for heavy work in a hot environment should be protected at first by restriction of labor and by liberal ingestion of salt. The same is true of workers in general when a heat-wave succeeds upon a period of cool weather.

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Chapter XXXVII

TROPICAL ULCER (TROPICAL SLOUGHING PHAGEDENA)

Synonyms.—*Ulcus Tropicum*, *Naga Sore.*

In many parts of the tropics one encounters a very great number of ulcerative processes of the skin. These lesions may be associated particularly with the presence of *Spirochaeta pallida* or of *Spirochaeta schaudinni* and of *Bacillus lepra* or *Leishmania tropica.* More rarely, ulcerative lesions are encountered which are associated with *Spirochaeta pertenuis* infection or are of blastomycotic or sporotrichial character. Granuloma inguinale and lymphogranuloma inguinale are also not infrequently observed in some localities.

Other cases of ulceration may be explained by infections with ordinary pyogenic organisms of the skin which are enabled to get a foothold in an abrasion or other minor wound, in a person whose resistance has been reduced by such cachexia-producing diseases as malaria, dysentery, or ancylostomiasis. Indeed some authorities attach special importance to the tibial ulcers found in advanced cases of hookworm disease. Some of the sores may be primarily due to irritating applications used by the natives of many countries as setons. In other instances, the sores may result from neglected wounds.

It therefore seems clear that the chronic ulcerations of the skin observed in the tropics may have at times a very different etiology. However, investigations during many years in different parts of the tropics seem to show that there is one very common form of ulceration known as tropical sloughing phagedena, or tropical ulcer, that may be regarded as at least a clinical entity and that has been reported in a few instances to have given rise to epidemic proportions.

Geographical Distribution.—It is the commonest form of ulceration in Amazonia and is also very common in most other countries of tropical South America. In Asia it prevails especially in India, Indo-China, southern China, and the Philippines. In most parts of Africa it is common. The writer found it also particularly in the Belgian Congo and in Tanganyika. Corkhill reports its prevalence in the Sudan, and Brennan, Anderson and Roberts in Kenya Colony. It is said to be the commonest cause of disability among laborers in Malaya, and James (1938) has emphasized that it is a terrible scourge in the islands of the southern Pacific, throughout Melanesia, and especially in New Guinea and the Solomon Islands, where he studied 892 cases. Manson-Bahr (1940) points out that it has occasionally assumed epidemic proportions. James (1938) refers to epidemics of such ulcers, especially in New Britain, Melan-

esia, and Lloyd Patterson has described an outbreak in Assam which swept like a plague through the country, seriously interfering with the efficiency of the labor forces in the tea plantations. Manson-Bahr states that it was very common among the carriers attached to the East African forces during the Great War, and among them and in the natives of Kenya, it caused an immense amount of disability. During 1943 an epidemic was reported in the civilian population in Algeria from August–December; 4,000 cases were reported. Many more cases were believed to have occurred. Amputation of the legs was necessary in at least 8 cases to save the lives of patients.

Etiology.—Although phagedenic ulceration is evidently an infectious condition, its etiology is not yet entirely clear. The most striking feature with reference to its cause is the presence of spirochaetes and fusiform bacilli in the lesions. These organisms are practically always associated during the active stage and the writer has found them not only upon the surface of the lesions but extending at times for at least several more centimeters into the tissues surrounding the ulcers. James, in a study of 892 cases, states that all showed fusiform bacilli, while 75 per cent showed spirochaetes and 65 per cent intermediate filamentous forms.

Vincent (1896) in a study of 40 out of 47 cases examined showed that spirochaetes and fusiform bacilli were encountered in enormous numbers in the pseudomembrane of the lesions where other bacteria were only occasionally encountered. He also found them later in a condition known as Vincent's angina.

Keysselitz and Mayer, who also found these organisms in tropical ulcer, considered the spiral organisms identical with *S. schaudinni*, which Prowazek described in 1907. (Synonym of *S. vincenti*, Blanchard, 1906.) Wolbach and Todd also encountered the spirochaetes, usually associated with fusiform bacilli, in 9 out of 20 ulcers. While the spirochaetes showed considerable variation in morphology, there was one type which was present in all of the smears in great numbers.

While the fusiform bacilli and spirochaetes are practically always found together, it is not yet definitely decided whether their association is a symbiosis or whether they represent different forms of the same organism. Some investigators, Tunnicliff, Smith (1932), James (1938), and others have observed an apparent transformation from one type into another in cultures. James emphasizes that sometimes preparations show every step between the fusiform bacillus and the spirochaete, via the presence of filamentous forms, as though they all represented actually only one organism. These filamentous forms may be long and rather thick and may be seen dividing to form fusiform bacilli, or they may be finer and show every gradation between a long, straight form and a definite spirochaete. Some of the filamentous forms are exceedingly fine. However, others believe that these two organisms represent distinct species. Both forms are obligate anaerobes and can be grown on enriched artificial media. Cultures have a foetid odor.

Tunnicliff has cultivated the fusiform bacilli anaerobically upon slants of ascitic fluid agar at 37.5°C. and observed that in such cultures, before the fifth day only bacilli can be found, but after this time spiral forms appear and finally constitute the majority of the organisms in the culture. Slanetz and Reddger (1933) and Spaulding (1937) have also cultivated

the organisms on a potato extract medium. The latter found that the spiral forms occurred rarely on this medium.

Tunnicliff and Hammond (1934) have studied the rough colonies of fusiform bacilli and have presented additional evidence to support the opinion that the fusiform bacilli and spirilla are different forms in the life cycle of one organism. Smith (1932) states that he has repeatedly seen spiral forms take the place of fusiform bacilli in pure culture and seen fusiform bacilli develop into spiral forms.

For convenience of description, the two forms are described separately.

Spirochaeta vincenti (*S. schaudinni*) (*Borrelia vincenti*) is a slender, delicate spirillum with a variable number of shallow and irregular undulations. In dark-field preparations from the lesions, they are actively motile. They stain readily with any of the silver impregnation methods (Fontana's stain), and with Giemsa's stain, but may also be demonstrated by slightly overstaining with dilute carbol fuchsin (1–5) or Loeffler's methylene blue.

Bacillus fusiformis is a coarse, plump, fusiform rod. The rods average from 5 to 7μ in length, but may vary beyond these limits in the same preparation. They may be straight or slightly curved, and the ends taper to a sharp or dull point. In stained preparations they are characteristically beaded or banded. They can be demonstrated with ordinary bacterial stains and are generally Gram-negative. They have been described as non-motile, but in some types a definite and even active motility has been observed.

Fusospirochaetosis.—In addition to tropical ulcer, the spirochaetal and fusiform organisms are found in small numbers in the mouths of many normal adults, particularly around the gingival margins and in the tonsillar crypts. They are very numerous in the pseudo-membranous ulcerative inflammations known as Vincent's angina and Vincent's stomatitis, and may complicate other types of ulceration, such as diphtheria, syphilis, or carcinoma.

Since the original description by Vincent of these organisms in cases of hospital gangrene, they have been found in a variety of pathological conditions associated with putrid inflammatory ulceration. The commonest sites are around the gums, tonsils, and mucous membrane of the mouth. The lesions may be confused with diphtheritic, syphilitic, or carcinomatous ulcerations, or the organisms may be present as secondary invaders of these conditions. From here extension may occur into the surrounding tissues, causing extensive necrosis, or into the middle ear, larynx, trachea, and bronchi. Less frequently any of the other mucous membranes may be involved—oesophagus, colon, appendix, and rectum. The external genitals may be the site of fusospirochaetal ulcerations, either as a primary infection, or secondary to syphilitic or chancroidal lesions. Deep phagedenic ulcers may result. Post-operative and other skin wounds may become infected. As pointed out above, many cases of tropical ulcer fall into this category. Finally the bronchi and lungs may be affected, with the development of a putrid bronchitis or bronchopneumonia (particularly post-operative) which is often followed by abscess

and gangrene. In these cases the organisms can be found in the sputum and their early recognition is imperative, since without appropriate therapy the mortality is high—40 per cent according to Kline and Berger. These organisms are frequently found in pyorrheal pockets, and although they may have no direct causal relationship to the condition, they undoubtedly aggravate it. Such areas when neglected have been aptly termed "anaerobic incubators." These organisms have often disappeared from the mouth after extraction of all the teeth.

Classification.—The genus *Fusobacterium* is defined in Bergey's Manual (1939) as follows: Gram-negative anerobic rods, usually with tapering

FIG. 235.—Area of necrotic tissue illustrating numerous spirochaetes and fusiform bacilli from a tropical ulcer, the active stage of which is shown in Fig. 236.

ends. Usually non-motile. Stain with more or less distinct granules. The type species is *Fusobacterium plauti-vincenti*.

D. T. Smith (1932) divided the fusiform bacilli into 3 types on the basis of their morphology. Type 1 is the characteristic large, fusiform bacillus commonly seen in Vincent's angina. Type 2 is similar, but thinner. Type 3 is smaller, usually straight, and is non-motile. This type was common in the pulmonary infections.

PATHOLOGY

A striking feature in the microscopical preparations made from the ulcers and examined either under the dark-field microscope or in specimens hardened and stained with Giemsa's solution, is the presence of large num-

bers of spirochaetes, identical morphologically with *Spirochaeta vincenti* or *S. schaudinni* and associated with the fusiform bacillus. In addition to these forms, in some instances one finds cocci and other bacilli, but only very rarely cocci in such abundance as the spirochaetes and fusiform

FIG. 236.—Section of tropical sloughing phagedena. Objective AA. Ocular 6.

bacilli. A study of sections of the ulcers shows that the tissues at the surface have usually undergone a coagulation necrosis. There is frequently a layer of coarsely meshed fibrin in which large numbers of degenerating polymorphonuclear leucocytes, spirochaetes, and fusiform bacteria are present. Other bacilli and cocci are also seen in much smaller

numbers. In films from a number of our cases of ulcer, phagocytosis of red cells by polymorphonuclear leucocytes had taken place. The epithelium surrounding the ulcers frequently shows thickening and downward growths, as is so often observed in other chronic ulcerative processes. Acantholysis is sometimes striking. The epithelium is often markedly infiltrated with polymorphonuclear leucocytes. The corium may be oedematous and infiltrated with polymorphonuclear leucocytes and with lymphoid and plasma cells, while the subpapillary layer often contains many fibroblasts. The walls and bases of the ulcerations consist of granulation tissue, the deeper tissues as well as the corium show a marked infiltration with lymphoid and plasma cells. Vertical sections of the ulcers reveal a large amount of granular detritus and numerous foci of leucocytic infiltration, while the deeper layer consists of more dense fibrous tissue. Spirochaetes and fusiform bacilli, and not infrequently other bacilli, are found, particularly in the areas where definite necrosis of the tissue has occurred. Fig. 235 illustrates the enormous numbers in which the spirochaetes and fusiform bacilli are often encountered in almost pure culture.

Method of Infection.—Although the fusospirochaetes are found so commonly in the ulcerative lesions, it is not yet entirely clear whether they are the sole primary etiological agent, or whether they are merely present as secondary invaders which modify and extend the lesions. The disease is not readily communicable to the lower animals by direct inoculation. The writer attempted to produce lesions in monkeys by removing small pieces of tissue from the ulcers and after they had been thoroughly rinsed in normal saline solution grinding them up in a mortar, suspending in saline solution, and the suspension injected subcutaneously into the animals. Suppurating and ulcerative lesions were produced in some of these animals, in which both spirochaetes and fusiform bacilli, as well as cocci, were found present. However, such lesions were only produced in those animals in which the skin had first been bruised or otherwise injured at the point of inoculation. From our observations and those made by other investigators it seems probable that the organism cannot usually establish itself in healthy skin, or even in many aseptic wounds, and that it is only when the integument is bruised, burned, or otherwise injured and the circulation interfered with, or the vitality of the tissues otherwise impaired that necrosis occurs and that phagedenic ulceration results.

More recently Kritchevsky and Seguin have stated they believe the organism to be primary and they have produced local abscesses in animals and occasionally a generalized spirochaetosis by the injection of pure cultures of spirochaetes and fusiform bacilli. When either alone were injected, no lesions were produced. The invasion of pyogenic cocci was believed to be a secondary phenomenon. E. Smith (1936) has also produced typical tropical ulcers in hedgehogs by intracutaneous and subcutaneous inoculations of material from human ulcers. Both fusiform and spirochaetal forms were found in the experimental ulcers. He believes that other anaerobic organisms, especially streptococci and

vibrios, may also be concerned in some of the infections. He was unable to produce lesions with cultures of any of the organisms separately, but only with mixtures of all of them. He has also shown the identity of the organisms from oral and from pulmonary lesions. By intratracheal injection into rabbits, he produced typical lung abscess or gangrene, both with sputum from human cases and with membrane from cases of Vincent's angina.

Epidemiology.—Infection in man is undoubtedly influenced by a number of circumstances. Thus filth, overcrowding and malnutrition predispose to tropical ulcer, which is probably frequently transmitted by direct contagion from man to man. Patients suffering from other wounds and occupying beds under unhygienic conditions and next to cases with tropical ulcer are said not infrequently to contract it, and evidence of the contagion is sometimes seen among school children who are in daily contact with one another. Sometimes the prick or scratch with an infected instrument may introduce the infection into the skin. A case of a nurse who had her arm accidentally scratched by an infected knife with which a tropical ulcer had been excised two hours before is of interest in this connection. Although the wound was immediately washed with a solution of lysol, a papule later appeared, which rapidly broke down into a typical ulcer.

Apostolides performed an artificial inoculation through the broken skin in two cases. In both of these cases *Spirochaeta schaudinni* and *Bacillus fusiformis* were obtained in the lesions. In one, the lesions apparently began 48 hours after the direct inoculation. Pampana inoculated pus taken a few minutes before from a tropical ulcer very rich in spirochaetes and fusiform bacilli into another patient suffering from a lacerated and bruised wound of the ankle which was shown to be free of spirochaetes or fusiform bacilli by repeated examination. The wound was dressed aseptically afterwards and for about a week no change was noticed. Twenty-nine days after the inoculation a typical tropical ulcer developed in the place of the former wound, and the first smear made from it showed numerous spirochaetes and fusiform bacilli. The ulcer healed subsequently under appropriate treatment.

Patterson has reported that by bandaging a swab smeared with the secretions from a typical sore on the surface of an abrasion on the skin from which the scab had been removed he succeeded in producing a characteristic sore.

James (1938) believes that he has demonstrated that the discharges from a phagedenic ulcer are actively infective and may transmit the infection to another part of the body by direct inoculation from the original lesion.

It has been observed that the disease in some localities attacks especially the undernourished and malaria stricken natives. Clements, in Melanesia, and James, in the Solomon Islands, believed that diet deficiencies, especially in vitamin B_2, as well as climatic factors and malaria. predispose to the infection. Nevertheless they consider that the fusiform spirochaetes play an important part in tissue destruction.

McCulloch reports the blood calcium content, blood sugar, and blood urea to be much diminished; probably as the result of deficient dietary.

Gokhole in the examination of 1,500 recruits, points out the absence of tropical ulcer in the Sandawe tribe, Tanganyika territory. Their diet consisted of meat, milk, cassava, sweet potato and dried fish, which should give a high blood calcium. He thinks this an explanation of their freedom. Since they do not eat vegetables the majority of the calcium in their diet is not reduced by the presence of oxylates. In other tribes in the same district with a diet low in calcium ulcerations were very common.

Charters found tropical ulcer confined to two Somali battalions whose food differed from that of the East Africans. The main dissimilarity between the two diets was a deficiency of vitamin A and riboflavin in that of the Somalis.

As the feet and legs are most exposed to injury, they are the most frequent locations of this form of ulceration. Nevertheless the arms or other parts of the body may sometimes be attacked. Since cracks and abrasions of the feet are common among the

FIG. 237.—Tropical ulcer, active stage, Amazonia.

people who go barefooted, it has been suggested that natives and Europeans might become infected from bruises when wading in stagnant or other water in the tropics. In fact, Plehn and Lenz believe polluted water to be the cause of the infection and Smits has held the opinion that humid earth in plantation drains carries the organism. However, experiments in the isolation of pathogenic spirochaetes in such localities have not yet been successful. Also, while spirochaetes have been observed in a number of mosquitoes and in diptera, especially *Simulium*, none of these have been demonstrated to possess pathogenic properties and to give rise on inoculation to ulcerative lesions. That flies may occasionally transmit the infection mechanically from one ulcer through an abrasion on the skin of a healthy individual is probable.

SYMPTOMS

If a lesion begins independently of any abrasion or trauma of the skin, the ulceration may be preceded by the formation of a vesicle. It soon ruptures, leaving a sloughing surface. In other instances a small papule may be first noticed, which soon becomes inflamed and ulcerates. Development of the lesion may be associated with pain, some fever, and constitutional disturbances. The ulceration extends rapidly in diameter

and depth through the skin and subcutaneous tissues, and if untreated a lesion anywhere from 5–10 cm. in diameter may result. The margin of these ulcerations are not generally undermined or raised to a striking extent. The base of the ulcer comes to consist of sloughing tissue and portions of this tissue are gradually cast off. The surface is often bathed with purulent material assuming a gray or greenish-gray appearance. On wiping away this exudate, areas of granulation tissue may be seen springing up in different portions of the base of the ulcer, or near the margins. In the course of a week or two, the sloughing process may cease. In other instances, the slough extends in depth and in some instances will destroy not only the superficial fascia but in some instances muscles, tendons, nerves and vessels and even the periosteum of the bone may become necrosed by the gangrenous process.

In such cases, in which the joints, bones, and large blood vessels are destroyed, even if the patient recovers, great deformity may result from the contracting cicatrices, or from ankylosis. James reports that in New Britain ulcers and other complications (toxaemia, deep sepsis and exhaustion) were the chief causes of deaths in the hospitals. To save life, urgent amputations were often necessary, though amputation proved risky because of extensive subcutaneous extension of the phagedenic process. In severe cases the formation of scar tissue is unfavorable for the prognosis, since it diminishes the blood supply in the new skin and even after healing, the lesions frequently break down.

Diagnosis

Laboratory diagnosis of fusospirochaetosis depends upon the demonstration of the organisms in stained smears or by dark-field illumination in perfectly fresh material. If any membrane is visible in the lesions it should be removed and preparations made from the depths of the ulcer. In regard to pulmonary disturbances, the fact that the organisms are present in small numbers in the mouths of many normal individuals must be remembered in interpreting the findings, and other pathological conditions to which they may be secondary should be excluded. Sputum must be examined when fresh, since the spirochaetes may be autolyzed within an hour, or two. The peculiar sickening, slightly sweetish odor to the breath in infections of the mouth and lungs may suggest the etiology. There is no increase in the granular leucocytes in the blood, and there is occasionally a marked lymphocytosis.

Treatment

Very satisfactory results in treatment have frequently been obtained with neosalvarsan or neoarsphenamine employed both locally and by injections. For local application of the ulcerations a 3 per cent solution of salvarsan or arsphenamine may be applied on a piece of cotton for 24 hours at a time. When healthy granulations appear, then mild antiseptic ointments, such as those containing boric acid, have been recommended. Corpus has treated 598 cases of chronic ulceration in the Philippines, in

FIG. 238.—Tropical sloughing phagedena, advanced stage, Amazonia.

In cases with pulmonary lesions, neosalvarsan or arsphenamine should be given intravenously as soon as the diagnosis is made.

Pampana has recommended particularly for the ulcers daily dressings of 1–1000 solution of acriflavine. He obtained excellent results, and after the fifth day of treatment bacilli and spirochaetes were very rare in the lesion, and the ulcers soon showed good granulations and healed in a short time afterward.

Several authors have recommended surgical treatment and the scraping away of all the sloughs and softened tissue with a Volkmann spoon, until a firm base of sound tissue has been obtained and the undermined edges of the skin cut away with scissors so as to leave no pockets. Such method of treatment, however, is very painful and is usually unnecessary. Excision with subsequent skin grafting may be recommended in suitable cases.

Van Nitsen and Wälravens succeeded in obtaining cultures of the fusiform bacillus which was a strict anaerobe on ascitic fluid covered with a layer of sterile paraffin. The growth contained an abundance of the associated bacteria, the fusiform bacillus, and the spirillum. Suspensions

of the associated bacteria were sterilized and a vaccine prepared. Doses of one fourth to one half, three fourths and one cubic centimeter were given at intervals of two days. Some 200 patients were treated in this way, but the authors found no improvement with the treatment, and pronounced it of no curative value.

More recently Pons has carried out vaccino-therapy in tropical ulcer, and found that the anti-spirilla vaccine had a rapid action on the phagedenic ulcer in all cases treated. Forty-eight hours after treatment was begun, all pain had ceased and the inflammation had disappeared. After 3 days there was no sign of necrosis, and after the fourth day cicatrization commenced. Complete cure of the ulcers was sometimes long, depending particularly on the general condition of the patient and the character of the lesion. Four to five injections were usually enough. Pons states that the organism isolated from the ulcers and used as an antigen differs somewhat from *Spirochaeta vincenti* in its dimensions and cultural properties, but he could not state whether or not antigenic properties existed which were common to both germs.

Pfannenstill has recommended the use of sodium iodide combined with hydrogen peroxide. In the case of an ulcer on the surface of the body or the limbs, he recommends sodium iodide in the average dose of 15 grs. two or three times a day. Larger doses, 60 grs. to 90 grs. a day, may be given, but entail some risk of iodism. Immediately after the first dose of the salt the local treatment with peroxide is commenced. The ulcer is covered by a layer of cotton wool, which is kept constantly soaked with the acidified peroxide solution, which is dropped upon it every tenth or fifteenth minute, or, if desired, more frequently. The strength of the peroxide solution should be 1 to 3 per cent, to which there should be added ¼ to ½ per cent of acetic acid. Pfannenstill believes that the sodium iodide, after being quickly absorbed into the blood, is carried to the ulcerated site. Here it meets the hydrogen peroxide, the iodine is set free, and being in the nascent state acts purely as a bactericide, the iodine being more readily freed, and to a greater extent, if the hydrogen peroxide is in acid solution. The blood contains most sodium iodide about one to two hours after its administration, so that this is the time when particular attention should be paid to soaking the wool with the peroxide solution. This method of treatment, however, is obviously not very practical in many tropical countries where tropical ulcer abounds.

Amaral has reported exceedingly successful results in Brazil by means of the local application of normal dried serum without the use of any antiseptic substance. He states that on the first application of the serum the ulcers begin to change in appearance, becoming clean and regular, and when the dressings are applied with care some of them become aseptic. An intense reaction of cicatrization is produced without delay and the sore begins at once to heal. A complete destruction of the spirochaetes and fusiform organisms occurs daily. Amaral considers this superior to all other methods of treatment. Various bismuth salts have been used both for local application and injection (Field 1940).

Houssiau has reported recently a case of three and one half months duration which was previously treated with local caustics and neosalvarsan injections without result. The ulcer, however, almost completely healed after 3 intramuscular injections on successive days of 3 cc. succinate of bismuth, followed by 2 further injections at 2 and 3 days interval. Local applications of bismuth hydroxide in oily suspension were employed concurrently.

Injections of antimony tartrate have usually not given particularly satisfactory results. Abraham, however, claims to have obtained satisfactory results with this drug in the treatment of Naga sore in the tea gardens in India. Abraham, however, states that these ulcers were of undetermined etiology, so that possibly they might not be correctly classified as phagedenic ulcer.

Generally speaking, the treatment with the organic arsenical compounds appears to be the most favorable one, with daily antiseptic cleansing and dressing of the lesion, and later strapping with elastoplast. Terdschanian has reported an excellent result in a case of 2 years standing from injections of neosalvarsan and local treatment of 10 per cent copper sulphate solution.

James (1938) has also employed copper sulphate in glycerin using as much as the glycerin will absorb. To each ounce of the resulting solution, he adds one dram of pure carbolic acid as an anesthetic. This solution is applied daily to bad ulcers until the surface feels hard and granular. In the early stages, small superficial ulcers, after cleansing, often heal by Morison's method with bismuth iodiform paste, aided by firm strapping with elastoplast. For larger ulcers, James believes in excision and immediate skin grafting.

Kerby advises that zinc ionization is valuable in stimulating the healing of chronic ulcers. For this purpose he advocates a 1 per cent solution of zinc sulphate at the rate of 2 ma. per square inch for 20–30 minutes. Many other methods of treatment have been recommended. Velupillary (1941) has reported especially successful results with the application of shark liver oil which he points out has a very high vitamin A content, to which the healing of the ulcers is attributed.

Good results were reported by Bayley in 1939 from sulfanilamide therapy. However, Manson Bahr (1939) reported two cases in which it had no effect. Earle (1940) in a more extensive trial of sulfanilamide, found it was of doubtful value in the long standing ulcers, but that it seemed to be of value in recent ulcerations and in the pre-ulcerative or vesicular stage. In the cases favorably influenced, local treatment was also employed with other drugs.

It has been suggested that saturated solutions of sulfanilamide (0.8) in normal saline solution might be employed locally for treatment. Herrell and Brown (1940) have reported encouraging results with it in the treatment of badly infected wounds. While the precise mechanism of the chemo-therapeutic action of sulfanilamide on bacteria is not entirely clear, the action of the drug in the wound may be modified by several factors. Destruction of tissue results in a breakdown of protein with the formation of peptone and the presence of peptone inhibits the heterostatic action of sulfanilamide. The destruction of tissue in tropical ulcer

is usually extensive, hence the drug will probably be of no value except in very early lesions. Sulfathiazole has also been recommended for local use. Lages (1941) has reported that sulfanilamide is of value in "epidemic" tropical ulcer provided it is applied locally and given by the mouth as well. He believes it is the combination of the two methods that is probably responsible for the favorable action.

In undernourished and cachectic individuals, attention to the diet is of importance, and a well balanced diet, including fresh vegetables and lime juice, should be provided. In cases in which there is evidence of malarial infection, quinine, of course, is indicated.

Treatment recently suggested in the present war includes the following: A bulletin from The War Office, London, April, 1943, recommends: 1. That the ulcer is completely exposed, i.e. all overlying tissue which tends to damm up discharges is removed. 2. The wound is bathed in hypertonic magnesium sulphate solution, probably isotonic solutions, are equally efficacious. 3. Sulfonamide powder from crushed sulfonamide tablets is applied to the ulcer. Generally about one-third of a tablet is required, i.e., 2½ gr. 4. Zinc oxide plaster is applied directly to the ulcer to cover it. 5. The wound is not dressed again for about 5 days. The advantages claimed are that healing takes place in 7–10 days. Much time and material (gauze, lint, wool, et cetera) are saved. Draining is little interferred with and admission to hospital is often avoided.

Grindlay (1944) states that following the evacuation from Burma in 1942, many cases of naga sore in Chinese, Indian and North Burma tribes-people were dressed daily by his hospital unit. For treatment he recommended: Immediate excision of all dead tissue in acute lesions with a sharp knife or sharp curved scissors; Daily cleansing of the lesion with soap and water and dressings with sterile gauze soaked with 25% glycerin solution of magnesium sulphate; dressings should be held firmly in place by roller bandages. When glycerin is not available a saturated aqueous solution of magnesium sulphate may be used and the dressings soaked with this at frequent intervals. Occasionally in the infected ulcers in natives magots were encountered. In such instances he remarks that if it is feared that all have not been removed the wound should be packed with gauze soaked in azochloramid in triacetin for one day. Azochloramid seems superior to magnesium sulphate glycerin in this one respect. Sulfonamide powder or crystals was rubbed into all surgically exposed tissues and the wounds packed with vaseline gauze. In some instances after wrapping the entire limb in a layer of cotton a plaster of paris cast was applied.

Veld Sore

Synonyms.—Desert sore; Barco rot.

A form of tropical ulcer has been described under the name of veld sore, which is common in various desert regions. It is frequent in north Australia and Queensland and affected the British troops in the Sudan and South African campaigns. It also was reported to have caused a considerable amount of disability in Gallipoli, Egypt, Palestine and Iraq during the great war. In South Africa, it has been observed especially in sportsmen and travelers.

These ulcerations may appear on the face, as well as on the dorsal surfaces of the hands or forearms, or on the lower extremities. They seem to arise from infections of abrasions of the exposed parts. In the early stages of the lesion, the diphtheria bacillus has been frequently isolated, and some of the cases have been followed by diphtheritic palsies. The lesions have at times been demonstrated to constitute a form of cutaneous diphtheria. Such cases were reported by Craig in the Sinai desert. The simultaneous existence of cases of ordinary faucial diphtheria should

make one suspicious of the real nature of such ulcerations. A diphtheritic ulceration of the skin may be more frequent than was formerly supposed.

However, the Klebs-Loeffler bacillus can be isolated with ease only from the primary lesions. In the chronic ulcerations, it is very difficult to recover it, as it is often overgrown by staphylococci and other suppurating organisms.*

Biggam (1942) also has observed that anal diphtheria is a more serious affection. In its initial appearance it may resemble a thrombosed haemorrhoid. The condition may be a definite hazard among troops in the desert.

The veld sore starts as a vesicle, which soon breaks down to form an erosion, which tends to spread. The pain is more marked than would be expected. In about 2 or 3 weeks a punched-out ulcer may result, which is covered with a dirty gray deposit—not distinctly membranous in character. The ulcer is very chronic and resists treatment with the usual applications, but, following injection of antidiphtheritic serum in the subcutaneous tissues near the sores there is often rather prompt response.

Scott saw numerous cases in the British troops in the World War.

Manson-Bahr states that the desert sores he observed among British troops occurred most frequently in men of mounted units and the rate of incidence coincided with that of a wide spread epidemic of faucial diphtheria.

SYMPTOMATOLOGY

These ulcers are most frequently found on the dorsum of the foot, over the shin, and about the external malleolus. More rarely they involve the dorsum of the hand or back of the wrist and occasionally the face. In the multiplicity of clinical descriptions from various parts of the tropics, two types of well developed ulceration have been especially noted.

One is that of a rather chronic ulcer, which slowly develops from a painless swelling, which is not unlike a gummatous process. Surrounding the swelling is a circumscribed, reddened, glazed area of skin. After two or three weeks the swelling begins to soften and a serous fluid exudes from its summit. Ulceration, with the frequent formation of a membrane-like deposit, now sets in and later on there results a more or less punched-out ulcer showing indurated margins. There may be no impairment in the health of those with this type of ulcer.

The other type is generally seen in persons who are much debilitated or suffering from some cachectic state. In the earliest stages these sores seem to resemble an area which has been excoriated and inoculated with vaccine virus, there being a rather dry, angry-looking spot of erythema. This within a few hours may be surrounded by a circle of vesicles beyond which is an encircling inflammatory areola.

There is marked subjective pain and tenderness. The serum from the vesicles at this stage may show few if any bacteria and the cellular contents are made up almost entirely of polymorphonuclear leucocytes.

* Biggam has also noted the occurrence of a second form of desert sore which is attributed to a haemolytic streptococcus. Some observers believe that this is the more common form encountered in the desert.

Within a few hours to one or two days the area within the ring of vesicles is converted into a dark gray to black pultaceous diphtheroid membrane which when detached shows underlying fungating granulations, covered with greenish-yellow pus. This membrane, if stripped off, tends to reform with great rapidity (twenty-four to forty-eight hours), and in many respects resembles the membrane of diphtheria except for its dark color. These ulcerations extend with great rapidity and even when showing a tendency to heal may suddenly, from a point along the margin, proceed to form a new area of ulceration, extending somewhat as would a ringworm. When the original site of ulceration fails to heal during a period of several weeks, the edges become rather indurated but do not show the punched-out or undermined characteristics of the first type. These cases last for months and are far more tantalizing than the former type of ulceration for the reason that from time to time they show a strong tendency to heal, the process clearing up almost entirely, when suddenly the former area of the ulceration is equalled or exceeded.

Whether all these ulcerations are primarily diphtheroid in origin is not clear. However, typical diphtheritic pareses or paralyses occurred as complications in 27 per cent of one series of cases. Paralysis of the palate, arms, and legs, and accommodation and paralysis of the iris, have been noted. In other cases, ataxia, loss of knee jerks, anaesthesia, and incoordination have been observed.

TREATMENT

Specific treatment recommended is anti-diphtheritic serum, at least 4000 units being injected subcutaneously in the vicinity of the sore. The sores should also be dressed at first with the same serum, or with weak disinfectants. Preparations of chlorinated lime and boric acid have been frequently recommended. A popular antiseptic used during the World War for local treatment was eusol, which was made by shaking up 12.5 grams of bleaching powder in a liter of water, then adding 12.5 grams of boric acid. After shaking again and allowing the mixture to stand a few hours, it was filtered, the clear solution being eusol. It should be kept in well stoppered bottles, or made fresh from day to day.

Many reports have been made regarding the prevalence of desert sore in the British troops in North Africa during the present World War. In these reports the bacteria encountered have usually been the pyogenic cocci and not the diphtheria bacillus. Rapport (1942) after treating 1,000 patients, points out that the skin is far more susceptible to injury in the climate of the desert and the condition is almost universal among troops there. New comers among the fair-skinned men being specially susceptible. The minimum amount of trauma results unfavorably in a breach of the skin surface and a desert sore frequently results. Bites due to flies, bugs and mosquitoes occasionally supperate and give rise to a sore. He believed prophylactic treatment should be primarily the provision of a diet comprehensive in essential material constituents, especially vitamin C. In the Army, ascorbic acid tablets (25 mg.)

1 tablet per man daily were administered and the covering of all cuts and abrasions so as to prevent the access of flies and sand. He found the following remedy generally effective; powdered sulfapyridine incorporated into paraffin molle flav. (3.5 gr. tablets of sulfapyridine to 2 oz. of paraffin molle flav.). This is applied locally and the dressing renewed after 3 days.

In cases in which the diphtheria bacillus has been found in the wound, in addition to serum treatment, it has been stated that C. diphtheriae is Penicillin-susceptible and it is suggested that the local therapy by continuous application of a solution containing 250 units to the cubic centimeter applied at the site might be of special value.

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Chapter XXXVIII

GRANULOMA VENEREUM

Synonyms.—Ulcerating granuloma of the pudenda, granuloma inguinale.

Definition.—An infective, ulcerating, granulomatous condition generally involving the pudenda and adjacent tissues and conveyed usually by sexual contact. In most cases there is no tendency towards spontaneous healing.

Geographical Distribution.—According to Daniels the disease was first described by Macleod in India under the designation "Serpiginous ulceration of the genitals." In 1896, Daniels and Conyers described it as a very painful, disfiguring and contagious disease occurring in both men and women in British Guiana. Since this time it has been reported by many investigators in most tropical countries and is today widely prevalent in parts of India, Guiana, Brazil (especially Amazonia), the West Indies, Puerto Rico, the Pacific Islands, and northern Australia. It is also common in southern China. In Africa, it has been reported on the West Coast and in the north and central districts. Numbers of cases have been observed in the southern United States in negroes and it is not uncommon among the negro population in New Orleans. DeVogel has reported that in some areas in the southern portion of Dutch New Guinea the disease occurs in epidemic form and has threatened the extinction of some of the local tribes. With reference to its distribution in India, Chopra (1936) has found that it is largely confined to the eastern side of the peninsula. However, while it is common in the hospitals in Madras, on the other hand it is rarely seen in the large skin outpatient department in the Calcutta School of Tropical Medicine.

Etiology

Donovan (1905) described short rod or oval organisms as the causative factor.* They were found in all parts of the ulcers but were particularly abundant in the deep portions where no other organisms were present. They were subsequently termed Donovan bodies and were first believed to be a species of *Protozoa*. By some they are regarded as bacterial in nature and are encountered in large numbers in large mononuclear cells present in the lesions. A number of investigators still regard the etiology of the disease as undetermined. Nevertheless the presence of these organisms is such a constant occurrence in the typical ulcerative lesions that one is not justified in making a diagnosis of the infection unless they are present.

* Naming it *Calymmatobacterium granulomatis*.

Flu in Surinam and Vianna and Aragao in Brazil also observed similar organisms within the large mononuclear cells from scrapings of the lesions. They reported the cultivation of the organism and noted its resemblance to Friedländer's bacillus. Walker, in 1918, also cultivated on Sabouraud's and other bacteriological media a bacillus that he believed, as had Flu, to belong to the group of so-called capsulated bacilli of which *Bacillus mucosus capsulatus*, Friedländer, was the type.

A number of cases have been studied in the United States from an etiological standpoint. In most of these cases the encapsulated organism has been found in the mononuclear cells. However, in a number of them in which this organism has been present attempts at cultivation have failed, and this has led some investigators to believe it doubtful that it represents a strain of the *Bacillus mucosus capsulatus* which is readily cultivable on general bacteriological media. Thus Johns, who studied 94 cases in the Charity Hospital in New Orleans was unable to cultivate it from any of his cases. He points out that while *Bacillus mucosus*

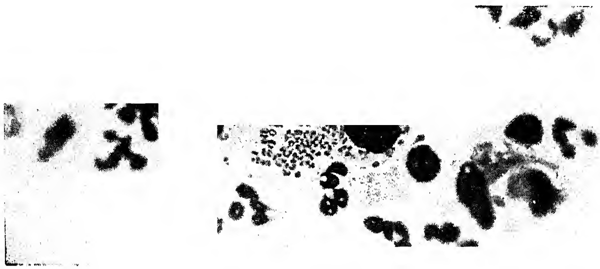

FIG. 239.—*Klebsiella granulomatis* (*Microbacterium capsulatum granulomae*). Tropical Institute, Leiden. (After Flu.)

capsulatus is pathogenic for laboratory animals the Donovan bodies were absolutely non-pathogenic for them as proved by injection of scrapings and tissue fragments and other implants from the human lesions.

Similar organisms have been found in the lesions of the condition known as rhinoscleroma and this bacillus has been termed *B. rhinoscleromatis*, being first described by B. Frisch in 1882. This organism, however, is apparently much easier to cultivate on ordinary bacteriological media than the organism of *Granuloma venereum*. Snijders in Sumatra thought that there might be close association between these two diseases.

McIntosh reported that he was successful in transmitting granuloma venereum from one individual to another and that he constantly found the presence of Donovan bodies in the experimental lesions. Campbell, however, contested this work of McIntosh, arguing that in the transplanted tissues other organisms might have been present. He was unable to transmit the disease by inoculating himself and other individuals and laboratory animals with cultures of the organisms he obtained from the lesions. Although Donovans organisms are almost constantly present some have suggested they may exert a symbiotic influence with the primary cause and represent a secondary invasion. F. L. Meleney and

several others have emphasized the importance of a non-haemolytic streptococcus in the production of the lesions.*

Symptoms

The infection is usually limited to the genital regions. A few cases have been reported in which the mouth was involved and the process invaded the face and neck. Torres reported an instance in which the disease subsequently attacked the upper lip and nose. Sidlick also noted ulcerations in the mouth of a typical case in which the disease started on the penis and then spread to the groins and right cheek. Lynch reported its occurrence on the back and on the legs. The disease has not been recorded as occurring before puberty. It occurs in both sexes, but more often in women, and this has been said to be the case especially where polyandry is practiced.

Fig. 240.—Ulcerating granuloma of the pudenda. Indian Case.

The incubation period is often short, from 2 to 8 days after sexual contact. In other instances the lesions have not been noticed until after 2 or 3 months following sexual intercourse. The primary lesion begins in the male usually on the penis, in the female on the labia minora, and consists of a small vesicle, papule or nodule which gradually extends over the skin and mucous membranes, new papules and nodules forming at the margins in the healthy skin. As the process extends, the thin epidermal layer may rub off, leaving an excoriated surface consisting of granulations that bleed easily and give off a creamy discharge, frequently very offensive. Suppurative ulceration usually occurs later.

The process extends from the penis to the groins by continuity and thence down the inner surfaces of the thigh. When the glans penis is involved, there may be a fungating growth suggestive of epithelioma. In the female, the infection extends from the labia minora into the vagina and also to the labia majora and thence to the perineum and peri-anal region. Recto-vaginal fistulae often result. The process extends more rapidly and markedly when invading mucous membranes.

* More convincing experiments have been performed by Greenblatt, Dienst, Pund and Tropin (1939) who have transmitted the disease to 3 volunteers by direct inoculation of fluid containing Donovan's bodies and have shown that it is doubtful if the organism has been cultivated.

When the granulomatous process is advancing, there is frequently cicatrization of the areas previously invaded, forming a scar tissue which breaks down easily. There is little pain or itching and the general health is not impaired. There is no enlargement of the lymphatic glands in the uncomplicated cases. Although the process extends by continuity, yet it may also pass to parts not in contact with the diseased area and at times by auto-inoculation. While healing of affected skin tends to occur, that of mucous membrane does not. There is usually very little tendency to deep ulceration.

The extension of the process is very slow, when invading skin surfaces, and there may be a history of years involved in the production of a large patch of scar tissue. At times, spots of active granulations may show on

FIG. 241.—Ulcerating granuloma of the pudenda. Philippine case

an area of glazed, unhealthy looking scar tissue. An abundant serous discharge which has a very offensive odor frequently occurs from the excoriated patches of skin.

In neither sex do the lymphatic glands become affected unless secondary infection occurs with streptococci or staphylococci. The infection remains a local one. Eventually large cicatricial lesions are formed. These, however, in untreated cases usually do not represent a healing stage, as the infection still shows a tendency to spread. In some instances, hypertrophic lesions result from an extensive fibrous reaction in the subcutaneous tissues, in which, however, foci of active involvement continues, due to the persistence of the infective organism. As a result of cicatrization, the lymph channels are sometimes blocked and pseudo-elephantiasis of the genetalia may occur. Manson-Bahr reports that impassable strictures of the urethra may result, and recto-vaginal fistulae. In such cases death may result from extension of the infection into the bladder, resulting in septic cystitis.

Pathology

The histological appearance of the lesions varies considerably. Usually the connective tissue of the corium swells and disappears and in its place one finds an extensive round cell infiltration which is often particularly diffuse in the central portions of the lesion. The diffuse cellular infiltration which is observed surrounding and below the central area is composed of polymorphonuclear leucocytes, lymphoid cells, endothelial leucocytes, and a few plasma and mast cells. Particularly at the periphery there are connective tissue cells. In areas of typical granulation tissue, numerous capillaries are observed, but there are no haemorrhages. Giant cells are usually not found. Near the margin of the lesions polymorphonuclear leucocytes are usually abundant, being found particularly in the papillary layer of the corium. In the reticular stratum, the polymorphonuclear leucocytes are usually in small numbers, endothelial leucocytes predominating, with a smaller number of lymphoid cells and plasma cells. The cells of the epidermis are swollen, often hyaline, and show mitosis. The papillae are usually found to be increased in length and in some instances penetrate downward into the papillary and reticular stratum. In the older lesions there is no caseation, but the tissue becomes oedematous and many fibroblasts and later much cicatricial connective tissue is found.

The most characteristic picture is the presence of numerous swollen mononuclear cells (endothelial phagocytes) containing large numbers of encapsulated rods (Donovan's organisms). Many of these cells are vacuolated and the organisms lie in the vacuoles. In some instances the cells present a foamy-like appearance. These cells have been described by Pund and Greenblatt (1938) as typical granuloma cells.

In the hypertrophic lesions there is an extensive fibrous reaction in the subcutaneous tissue, in which, however, small areas of active inflammation in which endothelial cells containing the organism are visible. In the cicatricial lesions, Von Haam (1940) describes the characteristic changes as consisting of thick bundles of collaginous fibrous tissue including still, small foci of inflammatory reaction, the collaginous tissue resembling closely the keloid masses often observed in the scars of negroes.

Gage suggests that owing to the abundant transformation of new connective tissue which constitutes one of the most important features of the lesions that the term sclerosing granuloma is more appropriate than ulcerating, as the ulceration seems to be insignificant in comparison with the formation of the dense fibrous tissue and deep scarring. In one case he observed that epithelial cells had become completely separated from the branching papillae of the epidermis and in one area he found pearl formations of these separated epithelial cells, the condition resembling a spino-cellular carcinoma.

Diagnosis

The diagnosis may be made by the demonstration of the characteristic organisms. Scrapings should be made from the ulcerations or other lesions

and stained with Giemsa or Wright's stain. The organisms are encapsulated and occur as either oval or diplococcoid in form, or as very short rods measuring about 1.5 by 2μ. They are Gram-negative. Usually they are enclosed in large mononuclear cells, but sometimes they may be found free in the preparation.

Pund and Greenblatt have employed silver stains for their demonstration. By silver impregnation methods, they appear as dark brown

FIG. 242.—Venereal granuloma. (After Martini.)

or black elongated, ovoid masses with intense bipolar staining. These organisms have been found in smears stained by Giemsa's solution in from 60 to 80 per cent of the cases. They are usually present in the active stages, but in the true healing scars they are sometimes no longer present or demonstrable. Von Haam (1940) has found them in every one of his cases in the active stages of the disease.

Clinically the disease must be distinguished from syphilitic ulcerations of the groin. The absence of general gland involvement and of secondary

manifestations of syphilis and the failure of antisyphilitic treatment are means of distinguishing the disease from syphilis. In the laboratory it may be distinguished from this disease by the presence of Donovan organisms and by the absence of the Wassermann reaction. In some respects it resembles lupus vulgaris, but it is not associated with the tubercle bacillus and there is an absence of giant cells and of tubercles and of caseation in the lesions.

Generally there should be no confusion with malignant disease. However, Pund and Greenblatt have reported upon a fungating form affecting the cervix in negresses which may resemble the ulcerative and vegetative type of carcinoma of the cervix. Its exmtree chronicity and the absence of cachexia do not suggest a malignant nature in most cases.

Treatment

Intravenous injections of tartar emetic were first employed in the treatment of granuloma inguinale in 1913, in Brazil, by Aragao, Vianna and de Souza-Araugo. This work was soon confirmed by Breinl and Priestly in the treatment of a case in Australia. The value of the drug in the treatment of this affection would appear to be undoubted. It is also recommended to apply locally compresses soaked with ½ per cent of tartar emetic. Some observers recommend the application of an ointment containing 1 per cent tartar emetic left on for 2 hours and then wiped off and boric acid ointment applied. Intermittent cleansing with eusol solution is advisable. Touching of exuberant granulations with silver nitrate sometimes promotes healing. Among more recent authors who have considered and emphasized the efficacy of antimony in the treatment of the disease are Randall, Small and Belk, Gage, Canopius, Schochet, Murdock, Chopra (1936), Manson-Bahr (1940), and others.

DeVogel, in the treatment of 573 cases in Dutch Guiana, reported that 86.1 per cent were cured after one series of injections, and 12.8 per cent after a second series. While the total amount of antimony necessary for a complete cure varies from case to case, it has been roughly estimated between 17 and 18 gr. However, some advanced cases have required 170 gr. to complete the cure. In the majority of cases, it is well to begin with a dose of 2 cc. of a 1 per cent solution, gradually increasing the dosage to 5–10 cc. at daily intervals. Randall recommended intravenous injections of triamide of antimony thioglycollic acid in 0.4 per cent solution, or sodium antimony thioglycollate in 0.5 to 1 per cent solution. Ten cases were successfully treated.

Occasionally, however, cases do not yield to antimony treatment.

Earle (1938) points out as a possible cause of antimony resistance that where the oedema fluid is rich in albumin the absorption of certain of the antimony compounds may be hindered so that the causative organisms of granuloma venereum are not reached at all. In 5 cases of the disease in which 4 were resistant to antimony treatment, the patients had apparently had previous lymphogranuloma inguinale infection and oedema of the infected areas.

In certain instances in which secondary infection with nonhaemolytic anaerobic streptococcal infections have occurred, as reported by Meleney, he has recommended treatment with the standard preparations of zinc peroxide, the active preparation being rubbed into the wound mixed with distilled water to give a consistency of 40 per cent cream. Also for the treatment of such cases, sulfanilamide therapy has been recommended and Ross has recorded striking action of such treatment in limiting the spread of the lesions.

Since some patients do not tolerate tartar emetic well when it is given intravenously, fouadin and trivalent compounds of antimony may be employed, and fouadin may be given intramuscularly and even subcutaneously with very negligible local reactions. The official dose is 1.6 cc., gradually increased to 5 cc. every day, or every alternate day, and a total of 40–50 cc. constitutes the complete treatment.

Surgical Treatment.—Scrapings and the application of the actual cautery have been recommended. Temporary improvement may be obtained, but the infection usually reappears in the scar tissue. Excision can usually only be successfully undertaken in the very early stages, following which skin grafting may be advisable. X-rays have been employed in early cases with good results. In other cases, such treatment has produced no favorable effects.

Prevention.—As the disease is evidently spread by sexual contact, prophylaxis depends upon the avoidance of sexual intercourse with native women liable to be or actually infected.

Rhinoscleroma has been reported in most parts of the world but at the present time is more common in many parts of the tropics. It takes the form of spontaneous, painless and very chronic inflammatory growths, which may occur in any part of the respiratory passages from the nostrils even down to the hilum of the lung. It has recently been noted in India by Rao and Menon where 6 cases were observed. In 4, the characteristic histological changes were seen and the organism *Bacillus* or *Klebsiella rhinoscleromatis* was present. In 1 case, the organism was isolated in culture. Kuilman (1941) has also reported a case from West Java.

The most satisfactory treatment is mainly surgical. Recently good results have been reported from x-rays or radium.

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Chapter XXXIX

CLIMATIC BUBO

Synonyms.—Tropical bubo, lymphogranuloma inguinale, poradenitis, Nicholas-Favre disease.

Definition.—A specific infectious venereal disease characterized by a transient primary lesion, often undetected, followed by a subacute lymphadenitis with eventual suppuration, formation of fistulae, and finally cicatricial healing. The suppurative state is usually accompanied by fever and general constitutional disturbances. It is due to a filtrable virus.

The name lymphogranuloma inguinale may be confusing, since it is so similar to that of another disease, granuloma inguinale, which is an infection with an entirely different etiology. Stannus (1933) proposed the name "sixth venereal disease" for lymphogranuloma inguinale to distinguish it from (1) syphilis, (2) gonorrhea, (3) chancroid, (4) Vincent's infection of the genitalia, (fusospirochaetosis), and (5) granuloma venereum.

A distinctive reaction known as Frei's skin test enables us to group under climatic bubo various clinical states which may or may not show inguinal buboes.

History and Geographical Distribution.—Scheube first employed the term "climatic bubo" to a type of adenitis terminating in suppuration not uncommon in tropical countries. Stitt (1929) points out that naval surgeons of various countries have for many years observed and been interested in its origin. It seemed to affect particularly the crews of ships. In earlier years it has been frequently confused with a mild infection known as ambulatory plague. It has long been recognized in the Far East and in Africa among European sailors. Numerous reports of its occurrence in India, China, Malaya, Japan, the Mediterranean, the West Indies and South America have been made. Finally its presence has been noted in Africa, and especially in the Belgian Congo, by Chesterman (1938). Durand, Nicholas and Favre (1913) reported upon the disease in France under the name "lymphogranuloma inguinale." It subsequently was found to be common in the United States, chiefly among the colored population. Cases have also been found to be not uncommon in England and in many parts of Europe. Hanschell (1938) has observed 130 cases in males in London, in all of which the infection was acquired in the tropics or subtropics.

Etiology

The Virus.—The first definite evidence that the etiological agent is a filtrable virus was reported by Hellerstrom and Wassen who showed that the intracerebral injection of certain species of monkeys with material

obtained from human lymph nodes gave rise to a meningo-encephalitis which could be transmitted in series after filtration through Berkefelt V or Chamberlain L_3 candles. Later it was shown that monkeys could be infected with the virus into the prepuce with subsequent enlargement of the inguinal lymph nodes. Findlay (1936) also produced infection experimentally by placing the infected material on the scarified skin.

Levaditi (1932) discovered that the virus of lymphogranuloma inguinale can be transmitted to mice by intracerebral inoculation. Virulent strains give rise to cerebral symptoms in mice 2–4 days after injection. In addition to the production of meningitis in monkeys and mice, such infection has been produced in the cat and in a number of rodents. Intracerebral inoculation of guinea pigs results in meningitic lesions in only a small percentage of the animals.

It has been found possible by subcutaneous injection of lymphogranuloma inguinale material to produce buboes in the groins of guinea pigs, but the infection tends to be a self-limiting infection, the swellings occurring about 2 days after inoculation and remaining palpable only from 10–14 days.

Reports have also been made of the isolation of the virus from inflamed rectal tissues and from an inflammatory condition of the colon by Levaditi (1935). It has also been transmitted to animals from a case of conjunctivitis by Levaditi (1936) and Pomhamm has isolated it from the cerebro-spinal fluid in 2 cases.

In regard to the presence of visible organisms in the virus, Gay and Prieto (1927) reported the presence of small cytoplasmic granules in the cells from inguinal buboes, 1μ or less in diameter, and often occurring in small clumps. These granules were also described and illustrated by Findlay, 1933. He suggested the possibility that they represented the virus. This possibility has now been increased by the work of Miyagawa and his colleagues (1936) and Findlay (1939).

The granules in stained preparations appear either single in pairs or in short chains. Sometimes arranged to form a circle. Less commonly they appear in dense clumps comprising hundreds of minute bodies. The dimensions of the virus as shown by filtration through graded colodion membranes are similar to those of vaccinia virus, namely 0.125μ to 0.175μ (Miyagawa, 1935; Broom and Findlay, 1936). The virus has been cultivated upon the chorioalantoic membrane in tissue culture (Miyagawa). Tamura (1934) by using Tyrodes solution with sterile animal tissue, also reports cultivation of the virus. Original cultures were made from filtrates from gland pus and repeated transfers made successfully. He noted that the cultural antigen gave as marked reaction as that of Frei. He also used this heated antigen therapeutically. (See Chapter XXV for classification of this organism.)

Pathology

The swollen glands at first may be just palpable. Later they sometimes become the size of a hen's egg. At first the glands are discrete and

not attached to the skin. Later on periadenitis may occur and they may become firmly attached to the surrounding tissues by inflammatory exudate. The overlying skin is intact as a rule, but at times a soft center may be felt in the otherwise hard gland and there may be much oedema of the surrounding tissues, sometimes resulting in elephantiasis. Knabe has reported an instance in which there was rupture from a lymphogranulomatous suppurating area into the urinary bladder.

The most striking histological appearance in sections of the early buboes consist of minute inflammatory foci scattered through the gland substance in which lymphocytes and later endothelial phagocytes, plasma cells, and eosinophiles are abundant. Still later, polymorpholeucocytes predominate and small abscesses form and necrosis of the glandular structure occurs. At the periphery there may be noted haemorrhagic infiltrations and oedema in the region of the peripheral sinuses, with formation of fibroblasts, fibrous connective tissue, and a few giant cells. In some instances, when an incision is made into the center of these glands a visible necrotic area is found. Cultures prepared on bacteriological media under aseptic conditions from the necrosed areas remain sterile. In many instances considerable pus is gradually formed within the gland, although the skin above remains unbroken.

The infection spreads by the lymphatics to the deeper glands, especially in the female, from the vagina and the anterior part of the vulva, and from these localities posteriorly to the rectum, resulting in the genito-ano-rectal syndrome, sometimes with ulceration. Fistulous tracts may form from which there exudes much clear, sticky, mucous fluid. Finally, sclerosis of the gland tissue may occur, leading to rectal stricture.

Stained microscopical preparations of the discharge, or of sections of the buboes, reveal that in the mononuclear or polymorphonuclear cells there are minute particles. With Giemsa's stain the larger ones take on a purplish tint, while with Casteneda's stain they assume a reddish purple tinge. Larger and smaller forms of the virus particles have been demonstrated extracellularly, forming compact, colony-like masses. The larger forms have been observed in considerable numbers, chiefly within 24 hours of intracerebral inoculation of animals. These virus particles were first noticed in the cells from inguinal buboes by Gay and Prieto in 1927, and by Findlay in 1933. Finally Miyagawa (1938) has brought forth additional evidence that they represent virus particles.

Clinical Observations

The disease is much more common in males than in females. Children have not been reported to suffer from it. Lymphogranuloma inguinale in the male is usually characterized by inguinal adenitis. Later elephantiasis of the genitals may occur, and rectal stricture is not rare. In the female, the characteristic lesions are esthiomene, chronic ulceration of the vulva, perineum, anus and rectum, fistula formation, and rectal stricture, their combination forming a genito-ano-rectal syndrome.

The Frei test has enabled us to group and recognize as forms of climatic bubo both the inguinal buboes so common in males and esthiomene (vulvar elephantiasis) and the genito-ano-rectal syndrome of females. Inguinal adenitis in the female is relatively rare but does occur. In man, the initial infection is usually of the coronal sulcus, and extends by the penile lymphatics into the inguinal glands and thence sometimes to the deep iliac glands. The latter usually do not suppurate. The intrapelvic glands however are rarely involved in the male. In the female, the intrapelvic glands are the ones usually involved, and this leads to peri-salpingitis, peri-rectal infection, and subsequent rectal stricture. The variation in form of the disease according to sex is particularly the result of conditions regarding the site of the inoculation and in the distribution of the lymphatic drainage, as the infection extends almost entirely by the lymphatics.

Vander Veer, et al. (1935) in 47 cases, noted 21 cases of rectal stricture—all in the female, and only 3 of these in the white race. The common location of the stricture was from 3–5 cm. from the external sphincter. In the Frei testing of prostitutes there may be obtained positive reactions in the absence of clinical signs in a small percentage of cases.

It has been stated by some observers that climatic bubo appears without an initial lesion, as is recognized for chancroidal, or gonorrheal buboes. But the present view is that there is a primary sore, which may even resemble a chancre, or be so small beneath the prepuce as not to be detected. Hanschell (1938) emphasizes that the primary lesion is frequently undetected. In his 130 cases in the male, it was observed in only 4. The lesion, when it does occur, has been described as a papule, vesicle, nodule, or small ulcer. In some instances it has been reported to appear from 3–5 days after coitus and is generally painless. In many cases it disappears in 7–8 days. In Hanschell's cases, however, the primary lesions were still present from 14–21 days after their first appearance. The swelling of the groin is usually noticed by the patient in from 1–3 weeks after the infecting coitus. Hanschell believes that the primary lesion of the woman's vagina probably persists for a much longer time than it does in the male. Chesterman (1938) found the primary lesion in women generally to be an ulcer on the labia or vestibule.

The disease has been divided roughly into 3 stages: the primary one, including the incubation period, extending from the time of infection and appearance of the primary lesion up to the symptoms pointing to infection of the lymphatic glands. The secondary stage representing the definite infection and swelling of such glands. In the male, it is especially the inguinal glands which become involved. In the female, the most usual early signs are of perirectal and retroperitoneal gland involvement and may not be noticed by the woman. In the groin, the lesions in men, and which are occasionally encountered in women in China, Japan and France, are characterized by stiffness and pain and swelling. The inflammation may be unilateral or bilateral. In some instances one groin is invaded

after the other. The reaction may subside without suppuration. However, the glands often suppurate and multiple areas of softening occur, followed by the production of many fistulae. The deep iliac glands also often show an increase in size and sometimes the lumbar ones, but with the exception of several cases in which the point of infection has been extra-genital the glands of other parts of the body, as the axillary and cervical, have not been involved.

In a large number of cases, the adenitis is accompanied by constitutional symptoms such as chills, sweats, fever, prostration, anorexia, nausea and vomiting, pains of the chest and muscles, stiffness of the neck, headache, epistaxis, and frequently bronchitis. The discharge of pus, or suppuration of new glands, may continue for a few weeks to many months or longer. In such cases the fever may be high and undulating, or typhoidal in character, and may persist for weeks as new nodes are involved. In some cases skin rashes have been reported, at times scarlatiniform or resembling those of erythema multiforme. Conjunctivitis and peripapillary oedema of the eyebrows have also been observed. In some instances rheumatic-like pains and painful effusions may occur in the larger joints during the pyrexial stages of tropical bubo. Healing of the inguinal glands, when it eventually occurs after several weeks, or in some instances months, gives rise to extensive formation of scar tissue.

The tertiary stage of the disease is characterized by chronic ulcerations, the formation of fistulae and of rectal stricture. In the female, it is not uncommon for the ulceration to give rise to a cloaca between the vagina and the rectum. Genital elephantiasis, particularly of the labia and vulva or penis and scrotum as a result of blocking of the lymphatics may also occur. In 3 out of 6 cases in women, Chesterman (1938) observed anal-vaginal fistulae. During the tertiary stage, death may occur from secondary infections.

Some observers have been doubtful as to whether all cases in which there has been a genito-ano-rectal syndrome or stricture of the rectum are cases of climatic bubo. However, Frei found that 80 per cent of such cases that he observed, gave a positive skin test.

Extra-genital infections have been recorded in a few instances. Curth has reported a primary infection of the tongue and lip, followed by glandular enlargements in the neck, while Hellerstrom has observed an infection in the glands of the axilla, and Lepinay and Grevin have described a primary infection of the foot. Hanschell (1938) has also reported an infection of the finger with the virus, with subsequent adenitis of the epitrochlear and axillary glands.

A number of human cases have been reported with symptoms of meningitic involvement, which is not surprising in view of the fact that a fatal meningitis may be produced by the inoculation of the virus into animals. Chevalier and Barnard (1932) have reported chronic meningismus in a woman with lymphogranuloma inguinale; the cerebro-spinal fluid showed the presence of an excessive number of cells and considerable albumin and gave a positive Frei reaction when injected intradermally.

Two other somewhat similar cases have also been reported and Rajam (1936) has recorded a fatal case of meningitis in which the cerebro-spinal fluid also gave a positive Frei test on intradermal injection. David and Loring (1935) observed epileptiform convulsions in a patient with ano-rectal lesions which had extended to the colon. It therefore would appear that just as in experimental animals the virus may also sometimes invade the human central nervous system.

Blood.—Examinations of the blood have shown that there may be characteristic biochemical changes such as a decrease in the lipin content and an increase in the percentage of free cholesterol (Rosen and his associates, 1937). Williams and Gutman (1936) have reported a hyperproteinaemia with an increase in the globulin and decrease in the albumin content of the serum. When the glands suppurate there is usually a leucocytosis.

Diagnosis

The disease must be differentiated from ulcerating granuloma (venereal bubo), chancroidal and syphilitic buboes, and from the ambulant form of mild plague. In Hongkong in earlier years the infection was frequently termed "pestis minor."

Plague buboes are usually exquisitely tender and the patient usually manifests signs of illness which are often extreme. Puncture of the bubo, if the case is one of plague, will reveal *Bacillus pestis*. The glands in climatic bubo are not exquisitely tender. In syphilis the glands are generally harder and the enlargement of the glands is usually general. The redness overlying the skin should usually differentiate the other venereal buboes. In the case of granuloma venereum, Donovan bodies are present.

More accurate diagnosis, however, may be determined by the following laboratory tests:

Diagnosis by the Frei Reaction.—Frei (1925) described an antigen prepared from the clear and sterilized pus of unruptured buboes of lymphogranuloma inguinale. The antigen is made by diluting material aspirated from buboes or an emulsion of infected mouse brain with 7 to 8 parts of saline. The mixture is heated at 60°C. for 90 minutes and on the succeeding day for 1 hour at 60°C.

The allergic state develops in from 2 to 4 weeks after the appearance of the bubo. The skin test is most marked after 24 to 48 hours and persists for 5 to 10 days. Some observers read the reaction after 2 days. It ranges from redness, with or without induration, to vesicle formation and the formation of a nodule. About 0.1 cc. is injected intracutaneously in the forearm—a saline control on the other side is advisable. Vander Veer considers the Frei test is best read after 4 to 5 days. Non-specific reactions usually subside after this interval. A positive result consists of the development of an inflammatory papule or nodule, at least 0.5 cm. in diameter, often with the appearance of a peripheral erythema and sometimes a central pustule, persisting for from 5 to 10 days.

In regard to the Frei test, Wassen (1935), in human cases experimentally infected, found that the test may become positive in 6–13 days after infection and may remain positive in some cases for a year, and in cases involving the rectum it persisted several years.

Hanschell obtained a reaction in a case 21 days after exposure to infection and found that it might persist for months. In one of his cases he found it was still present 12 months after discharge from the hospital. However, in 3 of his cases a negative result, that is an erythema only, was obtained 21–30 days after exposure but later, 42–51 days after infection the same antigen gave positive results, that is erythema and nodules.

Frei (1938) states that "on account of the possibility of generalized or focal reactions, it is not advisable to make the test in peracute stages of the disease, or in cases in which suppuration occurs near the perineum."

Nelson (1939) points out that the positive test is not proof of disease activity, for the test may remain positive for years after healing. According to Frei, it may be negative in the early stages, but will be positive in 95 per cent of the cases with bubo and 90 per cent of ulcerative elephantiasis. In the early stages, if the test is negative, pus from the patient injected into a known case of lymphogranuloma produces a positive test, but Frei advises caution in the use of this inverted test because of false reactions. Since only pus from unruptured buboes may be used, it is often difficult to secure the antigen. Therefore many investigators have attempted to produce antigens through inoculation of many animals, as mice, rabbits, guinea pigs, monkeys, dogs and goats.

Since mice are very susceptible to the virus by brain passage, the antigen has been especially prepared from the brains of such mice. The difficulty in the use of these animals lies in the fact that the virus cannot be easily standardized, nor is it known just how long it remains active.

Grace and Suskind (1936) have reported a method of standardizing mouse brain antigen so that it is as reliable as the Frei antigen. The virulence of the virus increases on mouse brain passage and with this increase the antigenic power is enhanced. Mice weighing 20 Gm. were inoculated with a suspension of virus of a virulence sufficient to kill from 85 to 100% of the mice in from 5 to 7 days. The brain of such a dying mouse was emulsified in sterile saline in such an amount that the heated product produced *a papule not less than 7 mm. in diameter* in an infected man. Using the eighty-eighth passage of the virus, they found that 0.1 cc. of a 1 in 13 dilution gave a papule varying from 7 to 10 mm. in diameter. When unstandardized mouse brain antigen was first used, there were reports of reactions with the brains of normal mice as well as of those containing virus, but these reactions of normal mouse brain did not give rise to a papule exceeding 5 mm. The products of tissue disintegration, whether in normal mouse brain or non-specific pus, are capable of producing a reaction on intradermal inoculation, but not equal to that of a virus-containing material.

There is, however, great difference of opinion at the present time as to the specificity and value of the mouse antigen for diagnosis. While

some have believed it specific, Straus and Howard (1936) and Brinkley and Love, obtained falsely positive and doubtful reactions. They also secured false positive reactions with normal mouse brain.

Findlay points out that a negative reaction with mouse virus may be due not to absence of infection in the individual but to failure of antigenic potency in the material injected.

Occasionally when the intradermal injection of 0.1 cc. of the antigen is negative, the injection of 0.3 cc. may produce a positive result.

Findlay has found if the antigen is filtered through a Berkefeld V filter the filtrate is still capable of producing a positive reaction, but passage through a Seitz K filter, which removes the greater number of elementary bodies, also greatly reduces or usually inhibits the antigenic capacity of the filtrate.

Rake and Shaffer (1940) have prepared inactivated suspensions of elementary bodies derived from the yolk-sac, and separated from tissue constituents by differential centrifugation, and such suspensions have been successfully employed as antigens for the Frei test and for the demonstration of complement-fixing properties in the serum of persons infected with the virus; in the latter test suspensions of virus from mouse-lung have also been used. They also obtained such reactions with Seitz EK disc filtrates and suggest the antigen may be present in the soluble state. Sulkin et al (1941) have also reported a new method in the preparation of an antigen which is said to give reliable results.

Nigg and Bowser (1943) believe that the complement fixing antigens are enhanced by treating the suspensions with phenol and subjecting them to boiling temperatures. This type of antigen is said to rule out at least some of the nonspecific reactions which occur in early syphilis.

Smadel, Wertman and Reagen have found that it is impossible to differentiate sharply between human psittacosis and lymphogranuloma by means of serological tests, though in some instances it is possible to establish that a given acute illness was caused by a member of this group of viruses.

Hanschell has carried out the control intradermal test, always in connection with the Dmelcos chancroid vaccine. In various forms of venereal disease other than climatic bubo, he only obtained negative reactions with the virus of climatic bubo. However, in some of his cases of climatic bubo the antigen has given repeatedly negative results and therefore he believes that no verdict should be given on the result of the skin test alone and that if negative, it should be repeated.

Several other tests have been described for diagnosis. The Wassen test consists of the production of a fatal encephalitis in mice by inoculation of the virus. Another intracerebral test in mice has been employed in which a mixture of one part of a 10 per cent suspension of infected mouse brain and two parts of the serum to be tested is inoculated intracerebrally into mice in doses of 0.3 cc. A control batch of mice is similarly inoculated with a mixture of normal serum and infected mouse brain. With an active virus, the mice injected with virus and normal serum should develop symptoms in from 5–10 days.

Treatment

Treatment of the disease is often not satisfactory. However, in mild cases there may be a rapid subsidence of the buboes after a few days' rest in bed, with no other treatment. In some cases wet compresses and light mercurial ointment inunctions over the bubo at night have apparently been of value. In the early stages of the infection, the inflamed gland, if discrete, may be excised. Manson-Bahr has reported notable success by

such a procedure. In cases in which there is fluctuation of the bubo indicating pus, Hanschell recommends that the bubo should be aspirated and the puncture then sealed with all aseptic care. Aspiration may have to be repeated on several occasions. The bubo should not be incised. He advises especially in these cases protein shock therapy with typhoid or paratyphoid vaccine. Manson-Bahr has also employed such treatment commencing with 50,000,000 given by the intravenous route and gradually increasing to 200,000,000 or 300,000,000, the injection being given every third day. He found that two or three reactions were usually required before the buboes dried up and the surrounding induration disappeared. Treatment should be combined always with rest in bed and with antiphlogistin dressings. Hanschell reports that by the intravenous injections of such typhoid vaccines, no other treatment was given in 85 per cent of his cases and after 4–6 weeks the patients were discharged. In the remaining 15 per cent, operation was advisable, consisting of excision of the affected glands. He points out that there may be difficulties in the operation and that the glands are often adherent to the spematic cord, femoral vein and the external iliac vein.

With reference to surgical procedures in advanced cases there is danger of the further spread of the infection through the lymphatics, and incisions into suppurating sinuses or the removal of large masses of lymphatic tissues may be very dangerous. Often excision of the mass when suppuration is present is not followed by clean and rapid healing.

Vaccine Therapy.—An attempt has been made to prepare a specific vaccine by excising portions of the affected glands which have been cut up into small pieces, dehydrated over calcium chloride, and suspended in saline solution. The suspension has been injected in increasing doses every second day. No reliable reports have so far been made of the value of this method. Bercovitz has advocated intensive treatment by subcutaneous injections of Frei antigen. However, he reports improvement was very slow.

Drug Treatment.—Hanschell states that there is no satisfactory evidence that any drug has any effect on the disease. Intravenous injections of tartar emetic have been employed for some years. Wolf and Van Cleve (1932) reported the best results with a 1 per cent solution of antimony potassium tartrate given intravenously twice a week. From 10–15 doses of from 5–10 cc. have been employed. Others have employed the pentavalent compounds of antimony, as stibenyl and stibosan. Solganal, either intramuscularly or intravenously, has been recommended and employed extensively in Germany. However, recent clinical and experimental observations in the treatment of diseased conditions with gold salts have emphasized their toxicity and the dangers from their use. Hartfall, Garland and Golvid (1937) in a review of 900 patients with rheumatoid arthritis treated with gold salts, found that 40 per cent showed toxic effects. Deaths from the use of such compounds have been reported by Goldhammer (1935) and Anderson and Palmer (1940) and there is no specific antidote known for such cases of poisoning. In view of these reports and of the toxic effects of the drug on experimental animals, such treatment must be recognized at least as dangerous although several

Chapter XL

DISEASES OF RARE OCCURRENCE OR OF DOUBTFUL ORIGIN

Sarcosporidiosis

Sarcosporidia are a group of muscle-inhabiting, spore-forming protozoa, the affinities of which are unknown. The species have been placed in a single genus (*Sarcocystis*). They are parasitic within the striated muscle fibres of many mammals (especially pigs, mice, sheep, cattle, and horses) and occasionally of birds. The sarcocysts (Miescher tubes) are elongated tubular bodies which distend the muscle fibers and may reach a length of 16 mm. The tubes are subdivided into numerous chambers which are filled with sickle- or oval-shaped spores (Rainey's corpuscles), 7 to 15μ long and 3 to 4μ wide. There is an enveloping capsule for the sarcocyst which may show striations. The life history is unknown. Mice can be infected by feeding them the spores. Heavy infections may be fatal, especially to mice, but light infections are harmless. In some places more than 50 per cent of the sheep and pigs may show infection. The parasite of sheep has been named *Sarcocystis tenella;* that of the ox, *S. blanchardi;* that of the mouse, *S. muris.*

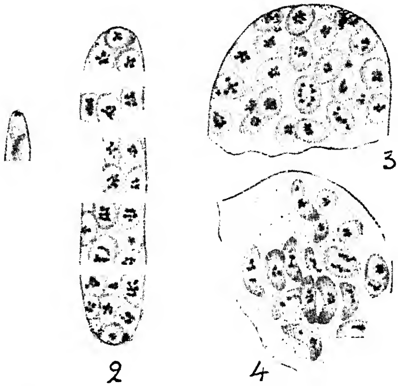

Fig. 243.—*Sarcocystis muris* in muscles of mice. (After Negri, 1910.)

1. Form 25 microns in length fifty days after feeding.
2. Form 52 microns in length fifty days after feeding.
3. Section of portion of a parasite fifty days after feeding.
4. Section of portion of a parasite sixty-eight days after feeding.

Pfeiffer (1891) found that a powerful toxin which in small doses would kill rabbits was secreted by *Sarcocystis muris.* He believed it was through this means that the parasite was able to penetrate the intestinal epithelium of the mouse, its normal host.

The parasite has been rarely found in man, there being only 10, apparently authentic cases reported. The first of these was reported by Lindemann (1868). Two were reported by Darling (1909, 1912), one by Lambert (1927), and one by Feng (1932). Hertig (1934) also reported a case in a child in which an organism found in the tissues appeared to be

They were not present in all sections of the myocardium, however, and in the first case only one invaded heart-muscle fiber was found after prolonged search. They say that staining of the organisms in the cytoplasm of cells requires further study. In many apparently well stained sections, the organisms appeared as homogeneous spherical eosinophilic bodies which could easily have been mistaken for colloid droplets or other structures of a nonspecific nature, while in other sections from the same paraffin block, stained somewhat differently, their structural detail was clearly visible.

In a study of human cases where the diagnosis has rested particularly upon the inoculation of the animal and the finding of *Toxoplasma* subsequently in the animal, Pinkerton has pointed out the danger of causing a prior latent infection with *Toxoplasma* to develop in the animal which was not demonstrable before.

Pinkerton and Weinman (1940) have also reported another case which they described as Toxoplasma infection in a Peruvian. However, this patient was also afflicted with *Bartonella* infection and had been given intravenous injections for treatment and at autopsy a secondary bacterial infection with cocci had occurred which was demonstrated both by films and by cultures.

As has been noted, organisms identical with *Toxoplasma* have been found to be very common in wild birds, but whether all the forms morphologically resembling *Toxoplasma* really are such has been questioned. At present, it is controversial as to whether certain forms which have been described in malaria infected birds are *Toxoplasma* or species of *Plasmodium*. Manwell (1939) has emphasized the difficulty of distinguishing between exoerythrocytic schizonts in bird malaria and developmental forms of *Toxoplasma*. The nature of at least some of the organisms reported in human cases as *Toxoplasma* is not entirely clear, nor has their relationship to protozoa, fungi or bacteria yet been clearly demonstrated.

Perrin (1943) has studied the pathology of experimental infections in animals and Weinman (1944) has especially studied the chronic infection in animals and he reports that sulfapyridine is strikingly successful in curing acute infections in mice.

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Onyalai

Onyalai is a disease which has occurred in parts of west, east and south Africa and is of obscure origin. It is characterized by the appearance of blood distended vesicles of the mucous membranes of the cheeks and hard palate. The tongue is often swollen. The skin may show haemorrhages and haematuria may be present. The blebs in the mouth may vary in size from 1–2 cm. A study of the blood shows that there may be some anaemia and in the fatal cases there is a sudden drop in the red blood corpuscles shortly before death. There is a marked decrease in the number of blood platelets. The blood shows a normal coagulation time but there is usually a prolongation of the bleeding time. There may be some fever. The disease usually engenders fear in the African natives in the districts where it occurs, owing to its sudden onset and high mortality.

Wellman reported its occurrence in West Africa in 1904. In Northern Rhodesia Wallace reports the disease is called "Chilopa" or "Akembe" (bleeding disease) while in the Congo it is known as "Kafindo." Wallace in Northern Rhodesia observed 15 cases annually. The onset was sudden and the early symptoms were lassitude, general dullness and suffusion of the conjunctivae with fever 103–104°F. followed by the wide spread hemorrhages.

Blackie (1937) notes that it occurs in Angola and Portuguese West Africa, Lualaba River and near Mt. Kenya, as well as in the Rhodesias. He studied 7 cases, one of which was fatal. The reduction of the red cells was rapid and was ascribed to loss of blood from mucous membranes and haemorrhagici nfiltration of tissues and organs. The anaemia was of the normal achromic type as met with generally, after severe acute haemorrhage. There was a remarkable reduction of the circulating platelets at the onset, these being reduced from the normal range of 250,000 to 500,000 per cmn. to between 20,000 and even less than 1,000. With this there was associated a marked prolongation of the bleeding time. Shelley (1938) has reported a case from Southern Rhodesia, where the man had been working in the mines for 6 years. He was of poor physique. There were haemorrhagic vesicles on the mucosa of the cheeks and soft palate and beneath the epithelium of the tongue. One was as large as 1 × ½ inch. The gums were soft and spongy. The red cells numbered 3,460,000. There were a few normoblasts. The white cells were 6000; the platelets 170,000 per cmm.; the reticulocytes 1.5 per cent; the haemoglobin 65 per cent. The bleeding time was 9½ minutes, or nearly 4 times normal, and the clotting time 4 minutes.

Gear (1938) has reported 7 cases occurring in South Africa; 3 ended fatally. Among the patients was one woman and the ages ranged between 20 and 40 years. Symptoms were practically the same in all: sudden onset with feeling of lassitude, then soreness of the tongue, gums and buccal mucosa, with rapid formation of "blood blisters" and profuse haemorrhage from the mouth, nose, and blood filled blebs or petechiae on the surface of the body. He notes that passage of blood in the urine and faeces may also occur.

In Gears cases the blood-filled bullae varied in size from that of a pea to 1½ inches in diameter. In some cases the eyes and face are suffused and swollen and the parotid glands enlarged and tender. Treatment by haemostatics is of little avail. The anaemia in severe cases is usually profound, and in fatal cases death may take place within a week.

At autopsy, all the organs and tissues show petechiae. In one of the cases reported by Gear (1938) a large cerebral haemorrhage was the immediate cause of death. Retroperitoneal, and perirenal haemorrhages and haemorrhagic broncho pneumonia are common. Gear reports also that the spleen may be a little enlarged and friable. He found that generally there is but little change from normal in the number of erythrocytes

best classified as *Sarcocystis* in which there also was a bacterial infection with a coccus.*

The human parasite has been designated as *S. lindemanni*. It is perhaps identical with one of the *Sarcosporidia* found in mammals. While the exact method of transmission of the parasite is unknown, as the mouse can be infected by feeding it the faeces of other mice infected with S. muris, it has been suggested that man becomes infected by food or drink contaminated with the faeces containing the parasite. The use of infected meat, according to the reports, seems to have no injurious effects. Probably the human infections are accidental.

Diagnosis has been made by the finding of the Meischer tubes in sections of the muscle. No specific treatment is known.

Craig (1940) points out there is little reason to regard the sarcosporidia as Protozoa and it is much more probable that they belong to the Fungi.

Toxoplasmosis

Toxoplasma was the term applied by Nicolle and Manceaux (1908) to a protozoan observed in a North African rodent, the gundi (Ctenodactylus gundi). They named the parasite *Toxoplasma gondii*. They believed it was distinct from *Leishmania*. Splendore (1908), in Brazil, reported a similar organism as present in the rabbit. Both these parasites were inoculable into pigeons. Shortly before, Laveran (1900) reported a similar parasite in sparrows. There have been reports since of the natural occurrence of a similar organism in a large number of animals, as wild birds and pigeons, the rabbit, guinea pig, mouse, rat, squirrel, dog and monkey, in many parts of the world, the diagnosis being based on the morphology of the organism found.

Sabin and Olitsky (1937) described the organism in North America as observed in guinea pigs. They isolated and maintained a highly pathogenic strain from this animal, and found that

(1) The strain was pathogenic for guinea pigs, mice, rabbits, rhesus monkeys, chicks and chickens; (2) multiplication was possible only within living cells, which included not only monocytes and endothelial cells but practically every type of parenchymal cell (liver, adrenals, lung, brain); (3) infection could be effected experimentally by the intracutaneous, subcutaneous, intracerebral, intravenous, intranasal and oral routes; and contact infection, studied in mice, occurred only when small numbers of starved animals were allowed to feed on others recently dead of the experimental disease; (4) neutralizing antibodies, which could be used not only as an index of infection but also as a means for identifying *Toxoplasma*, developed during the course of the disease in some animals (rhesus monkeys) but not in others (rabbits).

The organism was reported to consist of distinct cytoplasm and nuclear chromatin and was crescentic, pyriform, oval or round, measuring 6–7μ in length and 2–4μ in width, depending on the stage of development, as seen in fresh cover-slip preparations or in stained films. In fixed tissue sections they were not only smaller but also appeared different because of the shrinkage of the cytoplasm and nucleus. The chief taxonomic characteristic of the group, however, was the capacity to

* Gilmore, Kean and Posey (1942) have reported the twelfth case in which the parasites were found in the heart. (*Am. Jl. Trop. Med.* 22, 121, 1942.)

multiply and produce disease in a wide range of hosts, including mammals and birds.

Toxoplasma has been reported on a number of occasions as causing disease in man, but with inadequate and inconclusive criteria.

Castellani described bodies which he believed to be *Toxoplasma* in smears of the blood and spleen of a 14 year old boy from Ceylon who died of a disease characterized by severe anaemia, prolonged fever and splenomegaly. Fedorovitch found bodies similar to those reported by Castellani in blood smears of a 10 year old boy from the Black Sea district, who also had prolonged fever, anaemia and splenomegaly. Chalmers and Kamar also reported bodies similar to those of Castellani in a film of the spleen of a soldier in the Sudan, who, along with many others, suffered chiefly from chronic fever, headache, cough, and diarrhoea.

Wenyon (1926) doubts the reports of the human infections related above and says that it is perfectly clear in at least some of the instances that no such parasite as *Toxoplasma* existed. He points out that vegetable cells will often give rise to similar pictures and that such cells cocci or bacilli have been reported as toxoplasma and that such organisms may have invaded the body from the intestine after death.

Wolf and Cowen (1937) have reported a case of congenital granulomatous encephalomyelitis in an infant who died at 29 days of age. They reported parasites found with ease in the sections of the nervous system. They were smaller in size than those recorded for *Toxoplasma* and they named the organism *Encephalitozoon hominis*. Six other Toxoplasma infections have been reported in infants. In the case reported by Wolf, Cowen and Paige (1939), the parasite obtained was apparently similar to that found by Sabin and Olitsky.

Sabin (1941) has also reported 2 cases of atypical encephalitis occurring in boys 6 and 8 years of age. *Toxoplasma* was obtained in one and suggested evidence in the other. The chief pathologic change found in the nervous system, only after many sections from various regions had been searched, consisted of microscopic necrotic and granulomatous foci in the vicinity in which it was occasionally possible to find structures morphologically similar to *Toxoplasma*. Intracerebral and intra-abdominal inoculation of fresh brain suspension produced toxoplastic infection in 5 of 8 mice.

Pinkerton and Henderson (1941) have reported 2 cases of an acute, febrile, exanthematic disease in which the gross and microscopic appearances were remarkably similar to those of typhus and spotted fever. They point out that the clinical features of the disease in their two cases had almost nothing in common with those of the previously described cases of neonatal infection with *Toxoplasma*, their cases being essentially those of an acute, febrile exanthematic disease with atypical pulmonary involvement and, in fatal cases, death from respiratory embarrassment. In one of these cases, the bronchioles contained macrophages distended with the organisms, while in the other case a massive infection of the myocardial fibers with the parasite was seen, although the invaded fibers were not numerous and were unaccompanied by cellular infiltration.

of syphilis and in the scars of treponemiasis. It also occurs in pinta and has been reported in yaws.

In idiopathic vitiligo, any part of the body may be affected, including the muco-cutaneous areas, though the extensor surfaces of the hands, the face, trunk and legs are sites of predilection. Often the disturbance is symmetrical. The affection usually begins insidiously as a small, depigmented spot which may be diffuse or sharply circumscribed. The spots extend peripherally, increasing in number and usually coalesce. Usually the affection progresses slowly but in some cases it is so rapid that the greater portion of the limb, the trunk, or the face, may become white in the course of a few months. The hair of the affected parts may also become white.

FIG. 244.—Vitiligo, African native. (Harvard African Report, 1930.)

Chopra, who has found the affection very common in India, notes 4 clinical types: (1) affects the palms and soles only; (2) mucocutaneous type affects the lips and angles of the mouth, the eyelids, the anus or prepuce and the vulva; (3) only affecting the pressure area about the waist, where the loin cloth is worn by Indians; (4) a generalized type.

In a case here illustrated in a native African there were widespread pinkish-white patches on the hands, and, to a less degree, on the feet. The palms and heels were also markedly affected, but the largest lesion extended along the inner side of the right arm from the palm nearly to the elbow. There were small depigmented patches along the edges of the larger white areas and scattered over the body. A patch on the lip included part of the mucous membrane of the lip and of the gum. The skin of the back appeared normal in every respect save color. In the depigmented areas on the forearm, the skin was of normal texture, but exhibited irregular areas which were faintly reddish in color. On the hands, the skin seemed to be thickened and of abnormal texture. In some

areas there was slight scaling. On the palms and in the folds and about the joints there was more scaling and exfoliation of the horny layer, and pitting of the surface of the skin. Scrapings from the skin examined in potassium hydroxide solution showed no mycelia or spores of fungi. In stained preparations of scrapings made from the skin, the same result was obtained. Histological study of sections of skin from this case also show that the process is one of true vitiligo and that no fungi are present. In fact, the sections show no pathological changes with the exception of the absence of pigment. There is not only loss of pigment in all the chromophores, but also the whole area of skin in the affected patch takes a much paler stain in comparison with the normal skin seen at the edge of the tissue. Very few pigment-containing wandering cells are present in the corium. There is nothing from the microscopical or histological study to suggest that the affection is parasitic or infectious in its origin.

In the study of other cases, likewise, the only pathological change found was the absence of melanin and of melanoblasts, with sometimes an excessive amount of pigment at the margins of the white patches.

A form of vitiligo which may follow areas of prolonged infection with microsporon-furfur infection is sometimes encountered and has been called attention to in Africa by Shattuck and in the United States by Niles (1934). The depigmented areas which occur in leprosy are often not completely achromic. The depigmentation which occurs in pinta and yaws is discussed in Chapter XII. Leucoderma, in temperate climates, is sometimes associated with alopecia areata. The etiology of the acquired or idiopathic form is unknown. There is no evidence it is an infection. The individuals afflicted usually appear to be generally healthy. In many instances, heredity is apparently a factor.

In a few instances in which only a single patch has developed, recovery may in time occur. However, in cases of a few years' standing, there is apparently almost permanent loss of function of the melanoblasts.

Treatment.—It has generally been found that no treatment is of any avail. However, Panja and Maplestone (1940) have used the oil extracted from the seeds of *Psoralia corylifolia*, known as bouchi oil, by intradermal injection and have reported excellent results. In 2 or 3 weeks, pigment began to form. The white patches may be made less noticeable by the dilute solution of walnut juice, or by painting with permanganate of potash solution (0.2–0.5 per cent) in water. If the borders show hyperpigmentation, these may be bleached with strong hydrogen peroxide solution.

Vitiligo Reference

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Albinism

Albinism is not uncommon, particularly among the African tribes in the interior. The individuals usually have a dirty, white, transparent skin and yellow, or yellowish-white, or reddish-white hair. These patients usually appeared to be in poor physical condition, apathetic, and afflicted with photophobia and nystagmus. Such cases of *albinismus universalis* are usually regarded as congenital.

There is apparently a complete failure of the basal cells in oxidizing and storing melanin. Since the subjects are extremely susceptible to

sunlight and suffer from chronic solar dermatitis on the exposed parts, they should be kept away from the strong sunlight as much as possible.

A mild degree of the condition which has been observed in India sometimes results in a spotted skin, or actual piebaldism, but the condition may improve with the attainment of maturity, especially in the case of women after childbirth.

No form of treatment has been found efficacious, although an especially nutritious diet has been recommended by Chopra.

Keloid

This term has been applied to an hypertrophy of the fibrous tissues particularly in the cellular layers of the corium. Under usual conditions

Fig. 245.—Keloid, African native.

in the formation of scars, the fibrotic process becomes arrested apparently by the strangulation or obliteration of the newly formed blood vessels especially through contraction in the healing wound and there are left more or less pigmented, or depigmented, elastic scars which remain. However, if the development of newly formed blood vessels continues and there is an abnormal response of the angioblasts, the growth of fibrous tissue may continue, giving rise to hard overgrowths of tissue which become raised above the surface of the skin and may extend well beyond the original site of the injury. In many such instances, the epidermis over the keloid growth then becomes thin from pressure and the growth may have a smooth, glossy appearance. Sometimes there is considerable hyperaesthesia or actual neuritic pain owing to involvement of the sensory nerves. The growth, as a rule, takes place slowly and the lesions vary a good deal in size and distribution. Those occurring after burns or scalds are often extensive and may lead to contractures and disfigurement. They rarely involute spontaneously.

In the case illustrated, the lesions consisted of large, keloid-like nodular swellings on the sides of the neck, face, chest, breasts, shoulders, back, arms, legs and flanks. They were elevated from 0.5 to 1.5 cm. above the surrounding skin and the edges of some of them, particularly upon the back, bulged and spread out slightly over the under-

lying skin, so that they had a mushroom-like appearance. The diameter of the tumors varied from about 5 mm. to 15 mm. or more. Some of them had coalesced to form irregular masses. They were all sharply circumscribed, but some circular, while others were irregular in outline. Retraction of the swellings in the bend of the elbow had produced a contracture, so that the right arm was bent and fixed at an acute angle. The functions of both hands were impaired by scarring and with keloid formations on their backs.

Some of the nodules showed pitted scars and others more extensive scar formation in the center, but the smaller nodules exhibited little or no scarring. Some of the larger ones were covered by areas of normal skin, while over many of the other swellings the skin was tense, shiny and translucent in appearance. The color of the skin was not materially altered, but there was a lack of normal elasticity. The consistency was firm to hard and some of the large swellings pitted verys lightly on pressure. A watery secretion exuded from a crevice in one of the swellings and another crevice was crusted. The skin sensation was generally apparently normal. The lymphatic glands were not enlarged. Excision of portion of a nodule from the back caused pain, but one excised from an overhanging edge of another lesion caused no pain. The bleeding was slight.

Pieces of tissue excised from one of the larger tumors, were found to be of tough consistency and tendinous-white appearance, while the smaller tumor was of softer consistency and of a pale rose tint upon section. The tissues were hardened in Zenker's solution and in formalin. Film preparations made at the time from the cut section of the nodules showed upon examination that they were rich in cells, and in films stained with Giemsa's solution, on account of the richness in character of the cells, a sarcomatous condition was suggested. In a few of the films, blastomycetic forms were observed in some of the epithelial cells from the surface of the skin. However, the occurrence of *Blastomyces* in superficial layers of the corneal layer is not uncommon in many individuals in parts of Africa not afflicted with keloids. Mention is made of this fact because Legendre and Montel and Pons have reported upon cases of keloid formation where Blastomyces was believed to have had etiological significance.

The sections from the tumors of this case were stained in haematoxylin eosin, Giemsa's solution, Mallory's connective tissue stain, and Levaditi's silver impregnation method. A histological study of the 4 pieces of tissue removed showed that the lesions which lie beneath the epidermis are composed almost entirely of fibrous connective tissue. However, there were slight variations observed in the different tumors, and also in different parts of the sections of the same tumor.

Some of the waving connective tissue fibers were so thick as to resemble in size microfilariae. No elastic fibers could be distinguished in these areas, which is in marked contrast to what is usually observed in ordinary cutaneous scar tissue. In other places, the tissue was rich in long, spindle nuclei, and the growth otherwise consisted of dense, fibrous tissue, while in still other areas the fibroglia fibrils were distributed in thin strands between layers or bands of the coarser collagen fibers. These appearances were especially marked in the sections stained by Mallory's connective tissue stain. There were good numbers of blood vessels within the tumors, and in many areas there was slight infiltration and proliferations of the cells about them. However, the proliferation and infiltration was not marked and the infiltration did not extend into the surrounding tissue for any great distance. For the most part, the tumor was strikingly free from infiltration with cells. The proliferation of the fibroblasts was a much more striking feature than the proliferation of the vascular endothelium. On the whole, the tissues showed a marked regenerative process on the part of the fibroblasts, with little or no endothelial or lymphocytic infiltration.

The explanation for the marked tendency toward keloid growths among many African tribes is difficult. Sometimes an hereditary predisposition has been observed.

Justus believes there is some relationship between hyperthyreosis and keloid formation, while Payr believes that individuals with hypoplastic constitutions are especially predisposed to their formation, in fact to rich connective tissue formation in general.

PSYCHOPATHIC DISTURBANCES

Latah

Latah is a peculiar form or manifestation of hyper-impressionability. It has been referred to also as a psychosis or neurosis, which has been observed in the natives of the Philippines, the Malay Peninsula, Java, and the surrounding islands. It occurs in both sexes, somewhat more often in women, but children are rarely affected. It is apparently confined to the Malay Race. Palthe (1936) described it as a peculiar reaction to fright, in which the most striking symptoms are a clouding of consciousness, echolalia, and echopraxia.

In Batavia, he writes, a woman is called latah when by giving her a fright it is possible to throw her into such a condition that she repeats the words spoken to her with the intention that she *shall* do so, and imitates all actions performed before her with the purpose that she *shall* imitate them. In order to precipitate an attack in individuals subject to latah, it is usually only necessary to suddenly attract their attention or startle them, as by a sudden shout or cry or blow, and at the same time by pointing suddenly at them. This causes them to lose control of themselves and they will then execute and repeat any movements or gestures, or repeat any sounds made by the individual who startled them, no matter how fantastic they are, or how dangerous. During this hypnotic-like state, the victim is at the mercy of his prompter and he will involuntarily follow him blindly and yield to any of his comments or suggestions. Sometimes when the individual is suddenly frightened he will fall down in an attempt to imitate the movements and gestures of any people who may be in sight.

Usually some of the relatives or neighbors recognize the tendency in one of their number to suffer from attacks of latah, and sometimes they call the attention of the physician to the condition, as the subjects otherwise often appear to be normal mentally and physically. In other cases, the discovery of the condition by the physician may be an accident.

Such individuals are often made the subject of practical jokes. They, however, usually are aware that they are being made fun of and greatly resent it and become angry and often echolalic.

Palthe states that it is certainly not a psychosis and still less is it a form of hysteria. Those who are afflicted with it, he says, are otherwise mentally sound and can maintain their social position in their natural walk of life perfectly well in spite of the teasing to which they are often subjected.

When the attack has been started, the patient remains in the condition as long as the examiner or director occupies himself with the individual. At times, the patient will frequently begin the attack with an ejaculation of some obscene or meaningless word. If the patient is left alone, or talked with in a quiet, calming way, the condition usually subsides and the patient again behaves like a perfectly normal person.

In severe cases, following performances requiring much physical activity, the individuals may show signs of exhaustion or of swooning, which may end the time of the hypnotic-like attack.

Repond (1940) has made physical examinations of 9 patients which did not reveal any defect. All seemed to be in excellent general health, nor could he detect any sign of mental disorder such as, for example, schizophrenia. While the general mental state on an average was fairly

low, the intellectual level did not seem to differ materially from that of other natives.

While, as stated, latah has been classed by some authors with the hysterias, Repond disagrees and believes the mentality is not that of hysteric individuals. The subjects are pained at their condition and fight very hard against it. In some respects it has the nature of an obsession or anxiety neurosis. However, apart from their ectokinetic crises, they exhibit no tendency to phobias or obsessions and anxiety is not the usual state of these patients. However, there seems to exist a certain state of anxious tension readily set free, though there does not appear to be any relation between the external excitant and the intensity and extent of the distress phenomenon of latah.

Palthe, who has had a wide experience with the disease in Malaya, also agrees that it is certainly not a psychosis and still less is it hysteric. He thinks a hypersensitiveness for impressions of fright exists in all cases.

A condition similar in some respects has been described among the primitive Ainu people and is known as "inu." It occurs usually in women and the attacks are precipitated by some emotional shock. They are of a psycho-motor character, and if one is startled into an attack she will continue to echo everything that is said to her.

Castellani, in his study of latah, divided all disturbances into two varieties; the impulsive and the mimetic. The former, which is produced by sudden shock, resulted in violent action or to language of which the patient might be very much ashamed. The mimetic is the form in which the sufferer, no matter how unwilling, is compelled to imitate. He suggests that latah may be closely related to the curious psychical phenomena seen at times among different races of afflicted people, being variously known in Europe as "the jumpers," "the barkers," and "the jerks," and that it may also be allied to those states of excitement into which people pass during times of religious revivals.

In Madagascar, 1863–64, among the people of the lowest classes at the time of the violent death of the king when sudden changes were made in the religion and laws, an outbreak occurred which is said to have been identical with the dancing mania of the middle ages. There is a strong admixture of Malay blood in the natives of Madagascar, especially in the ruling classes.

Unless unusual accidents occur, latah is not fatal, but it is apparently more or less permanent and it is incurable. However, it does not appear to grow progressively worse.

Auto-suggestion has been advised in treatment.

Latah References

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Amok

Amok is a well known native name in all Malaysian tropics and is applied to a form of homicidal mania which attacks Malays and leads to a blind fury to kill without reason. An individual will suddenly and apparently without reason seize a kris or knife, rush from his house into

the street, and slash and cut and stab at everybody he meets until he is overpowered or killed, or kills himself.

Not infrequently, in an incredibly short time, he will, with marvelous skill, deal deadly stabs, killing or leaving desperately wounded on the ground, 5 or 6 or even more people. In his lust and behaving somewhat like a mad dog, he attacks not only man but animals, such as the carabao (water buffalo) which may come in his path, making huge slashes in their sides. The neighbors, with wild cries of "Amok, amok," seek safety in rapid flight. Usually he is shot down by arriving police or constabulary, and if this does not come speedily, when there is no one in sight to kill, he may turn his spirit to destroy upon himself and self-inflict terrible wounds, such as cutting his throat or laying his abdomen widely open. In other instances, he swoons into a stuporous condition and has afterward no memory of what has happened. However, more often he does not become satiated and does not stop of his own volition. This is generally well known in the neighborhood and for this reason he is generally quickly shot, or killed in another way, so that as a rule a psychical examination cannot be obtained.

Hence for a long time the reason for such aggressive brain storms has not been clear and even now a number of observers do not think that an entirely satisfactory explanation can be given. These frenzies were formerly regarded as due to sudden insanity. Others suggested that a typical attack might be the result of circumstances such as domestic jealousy or gambling losses which render a Malay desperate and weary of his life and that hence it might be equivalent to a form of suicide.

Van Loom thought the attacks might be a specific reaction of the Malay race to toxic influences of the central nervous system, the result of attacks of fever caused by malaria, pneumonia or syphilis. However, this idea has not been supported in recent years, since the attack has been unmistakably observed to occur in subjects which were otherwise perfectly normal, both physically and mentally. Rather did the attacks appear to be the result of psychic influences and to occur in individuals which felt themselves violently offended or who were in serious trouble from which there seemed no outlet.

Palthe, (1936) who has especially studied the condition in the Dutch East Indies points out that an unsupportable conflict may develop in such individuals in which after a period of meditation there is an emotional overflow of his entire consciousness which discharges itself in an aggressive brainstorm. In cases in which the individual has come through the attacks still alive, he has found no psychic abnormality except a complete amnesia of the occurrence.

Van Loom has pointed out that anxiety is an element that is never absent in amok. He thinks that the individual gives the impression of a cornered rat, which strives to defend itself as best it may by making a savage and reckless attack on whatever may be in front of it. Several investigators have found that the individual may prepare himself, so to speak, for his actions during a period of meditation and the monotonous muttering of Koran texts with rhythmical swaying of the body and with dulling and narrowing of consciousness. Castellani also thought that the exciting cause was a strong emotion following anger, sorrow or hate and that if the individual recovered there was a period of depression lasting days or weeks during which the patient broods over his wrong. Miall thought that the attacks were sometimes due to smoking hashish. In the Dutch East Indies, it has been said to sometimes follow opium smoking.

Palthe regards it as being a standardized form of emotional explosion which is recognized in Malayan countries, a sort of beaten track, well

recognized and in certain instances fully expected by the person involved and his neighbors. He points out that it is a preformed reaction method that lies ready to hand, in which there is a certain ritual as it were, every phase being standardized. He has never known of a single case of amok among the many Malays who have gone to live in Europe. He importantly points out that the surroundings and sphere of influence in which the individual lives within the Malaysian land where the condition occurs has a definite influence on the frequency of amok and gives as an example that in the old hospital in Batavia, with its typical primitive native atmosphere, amok was quite common. However, when the patients were transferred in 1914 to an imposing, modern hospital, with up to date equipment, where everything was conducted on European lines and where an entirely different tone was maintained, from that moment amok among the patients ceased.

The results in the Philippine Islands have been somewhat similar. Here amok has been very largely observed among the Moro tribes that inhabit Jolo. The Moros of the Philippines were fanatical Mohammedans and had adhered to the belief that there is no God but Allah. In the early days of occupation of the Islands by the United States, amok was very common and numbers of officers and enlisted men, as well as civilians, lost their lives in these sudden, furious attacks which were so frequent. From a study of the subject, it appeared that in a number of instances such attacks had followed exhortations by the priests, or visits to them, shortly or immediately before. Through punishment of these Mohammedan priests, the disarmament of the Moros, and especially through their general education and through the training in the Christian Moro school established by the late Bishop Brent, such attacks began sensibly to diminish.

Especially through this school, there was brought to these neglected people the assets of a new civilization which raised their standards of living and, through leading better lives, their religious, social and moral views were changed. So great has been the change among these people within 25 years that amok is no longer a menace there and, indeed, one seldom hears of it in this locality.

Koro

A form of anxiety neurosis described in most text books of tropical diseases has been termed koro. This peculiar phobia has been described as appearing particularly among the Buginese and Macassarans in the Celebes and in West Borneo. It also occurs among the Chinese and is known by the term "*shook yong.*"

The condition has been described by Palthe as an anxiety state in which the patient is in terror that his penis will shoot into his belly, and that as a result of this he will die. This anxiety comes on suddenly, is very intense, and sometimes may last for several days on end. In order to prevent the occurrence that he so greatly dreads, the patient holds onto his organ with a vice-like grip, and is helped herein by his wife, friends and relatives, who sit around him in a circle. They must all see to it that the penis is not released for a single instant; otherwise, in it shoots and death follows inevitably! After long, weary hours of vigil, such an attack gradually wears off, but is repeated again and again.

such as the production of adhesions. Menes, however, thinks that scrofula and syphilis predispose to keloids.

None of these explanations except hereditary and racial tendencies seem to be particularly applicable to the frequent occurrence of the condition among certain African peoples. Keloids frequently develop at the time of puberty, or in the years immediately following.

Treatment with X-rays has been recommended, in which, however, severe reactions should be avoided and moderate applications given over a longer period of time. For small keloids, repeated refrigerations with carbon dioxide snow have been employed. Macleod has shown the use of radium to be most effective. He recommends a full strength radium plate which is screened off by a silver plate 1 mm. in thickness. He says the exposure should be one of 18–30 hours. However, the larger growths are often recalcitrant to treatment.

Excision is generally not advised, although Chopra thinks that in some cases very resistant to X-ray and radium that a plastic operation with skin grafting may be the best remedy. The result after surgical operation depends especially upon the inherent tendency to reproduce keloid growths.

Ainhum

This disease, equivalent clinically to a spontaneous amputation of the little toe, has been chiefly noted in the natives of the West Coast of Africa, especially among the Kroomen and in Brazil. The writer found it common in Liberia, where it might be unilateral or bilateral and occasionally caused the loss of the 4th toe as well as the 5th. Cases have been reported from the West Indies and rarely from the Southern States of the United States. It does not attack white people and the susceptibility of black races is probably connected with their tendency to keloid development. There is some evidence of ainhum being a familial disease, as it sometimes seems to select members of the same family, or generations of the same family.

There have been all sorts of suggestions as to etiology: (*a*) that it is related to leprosy, (*b*) that it is a tropho-neurosis, (*c*) that it results from wearing constricting bands or rings on the toe, (*d*) that it is connected with frequent injuries to the under surface of the little toe.

Pathologically there is often found a fibrous cord which has replaced the bony structures normally attaching the toe to the foot. According to Unna, there is a ringform sclerodermia with thickening of the epidermis causing an endarteritis with the production of a rarefying osteitis. The disease is chiefly found in male adults between 25 and 30 years of age. Castellani, who has observed similar changes to Unna, also points out that the constant irritation causes the epithelium to proliferate internally and depress the skin, and the fibrous connective tissue of the cutis to become increased in quantity.

Spinzig (1939) who has discussed its occurrence in the United States points out its extreme rarity in any but negroes and that the constriction of the little toe is probably induced by some mechanical or infectious injury and that it predominates in negroes because of the marked fibrogenetic tendency which is so characteristic in some members of this race.

Davies and Hewer (1941) have reported a case in which a histological study was made of the tissues. The authors thouget than an epidermophytosis might be the

The course of the disease extends over several years, if the toe is not amputated by cutting through the fibrous pedicle, or as the result of ulceration from injury to the pedicle. There is little or no pain of the affected toe or toes, probably connected with loss of sensation.

Big Heel.—Maclean observed in natives of the Gold Coast an hypertrophy of the os calcis. Maxwell also described a similar condition in Formosa. It has been suggested that the condition may be similar to that which involves the superior maxillary bones in Gondou (see Chap. XI also Appendix p. 1627). Big heel is said to begin rather suddenly with fever, pain and tenderness followed by swelling and enlargement of the os calcis of one or of both heels.

Chiufa (Kanyemba).—Under these terms Manson referred to a form of acute rectitis which was reported from South America and later by Gilkes in Northern Rhodesia in valleys at an altitude of 2000–2500 feet. Recently it has again been called attention to in Africa. Manson-Bahr (1940) describes the condition with sudden onset and an acute course the primary manifestation being a white powdery condition appearing about the anus and giving the appearance of "boraccic acid or flour." In women the vulva may show a similar appearance. The patient then becomes acutely ill with pains in the back and fever to 104°F. The rectum then becomes greatly reddened and swollen and the inflammatory condition ascends upward to the colon. Diarrhoea and vomiting may also occur. The cause of the condition is unknown.

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under different names. Several other species are described in 7 different genera while the genus Candida he subdivides into 13 genera containing 122 species. Castellani in his classification has on a number of occasions described the same fungus under a number of different names. Such examples emphasize the difficulties in classification.

STUDY AND CLASSIFICATION OF MOULDS

Classification of More Important Fungi Pathogenic for Man

Class	Family	Genus	Species
		Absidia	A. corymbifera
		Mucor	M. mucedo
Phycomycetes	Mucoraceae		R. niger
		Rhizopus	R. parasiticus
	Ashbyaceae	Piedraia	P. hortai
			P. colombiana
	Coccidioideaceae	Coccidioides	C. immitis
		Rhinosporidium	R. seeberi
		Histoplasma	H. capsulatum
	Eremascaceae	Zymonema	Z. dermatitidis (Cryptococcus gilchristi)
Ascomycetes			Z. capsulatum
	Eremascaceae Imperfectae	Castellania	C. tropicalis
			C. pulmonalis
		Syringospora	S. albicans
			S. psilosis
			S. interdigitalis
	Saccharomycetaceae Imperfectae	Cryptococcus	C. histolyticus
			C. meningitidis
		Malassezia	M. furfur
	Trichophytoneae	Trichophyton	T. tonsurans
			T. sabouraudi
		Megatrichophyton	M. roseum
		Ectotrichophyton	E. mentagrophytes
		Microsporum	M. audouini
		Achorion	A. schoenleini
			A. muris
		Epidermophyton	E. interdigitale
			E. floccosum
		Endodermophyton	E. concentricum
	Aspergillaceae	Aspergillus	A. fumigatus
		Penicillium	P. bertai
		Scopulariopsis	S. brevicaulis
Fungi Imperfecti		Allescheria	A. boydii
	Toruleae	Dematium	D. wernecki
		Madurella	M. mycetomi
		Indiella	I. brumpti
	Dermatiaceae	Hormodendrum	H. pedrosoi
			Phialophora verrucosa
	Actinomyceteae	Actinomyces	A. bovis
			A. madurae
			A. asteroides
			A. minutissimus
			A. thuillieri
	Sporotrichieae	Sporotrichum	S. schencki
			S. beurmanni
		Aleurisma	A. albiciscans

Morphology and Biology.—Two classes of thallophytes are especially of medical interest; the Ascomycetes and the Hyphomycetes, or Fungi Imperfecti. A third class, the Phycomycetes, have only been reported from man in a few instances. The two latter not infrequently contaminate bacterial cultures.

Fungi, like bacteria, do not contain chlorophyll, hence they must live a saprophytic or parasitic existence. In their simplest form they consist of ramifying filaments called hyphae. A network made up of vegetative hyphae, intertwined in tangled threads, is termed the mycelium. Growth may be either by addition of new hyphae (apical growth) or by division in a single hypha (intercalary growth). The hypha may be a single cell or many cells separated by septa.

Some hyphae contain cellulose, others chitin. In some fungi the mycelium becomes packed as hard masses, containing food material to serve future germination, and known as sclerotia.

Probably only in the case of *Piedraia hortai* (causing a disease of the hair) are such structures present in pathogenic fungi, but in the mycetomas the granules are of this nature, and known as bulbils. Ergot is the sclerotium of a fungus (*Claviceps purpurea*) attacking the grain-bearing heads of rye, and is of importance medicinally and as a food poison. In the Middle Ages there were great epidemics of ergotism, causing gangrene (St. Anthony's fire).

Spores.—Equally important in structure with the hyphae are the spores (conidia). A spore may be simply defined as a cell which may or may not separate from the hypha, but which is capable of germinating and reproducing the parent cell or hypha. A spore may be non-sexually produced by simple separation from the hypha (conidium), development along the course of the hypha (oidium or chlamydospore), or within the protoplasm of the hypha (endospore). The term chlamydospore usually implies a rather thick walled asexual spore, which is capable of resisting an unfavorable environment and, subsequently, germinating. Hyphae may separate from parent hyphae and form arthrospores (thallospores), which may subsequently become oval or round (blastospores). Blastospores, characteristically, sprout from hyphae.

Certain fungi have hyphae which form fruiting branches called conidiophores (sporophores). When cells are present which give rise to endogenous spores (sporangia), the sporophore is called a sporangiophore.

The class Ascomycetes is characterized by the ascus, a sporangium in which spores develop usually to form 8 ascospores.

Where reproduction is of a sexual type, the gametes (sexual cells) may be equal or unequal, or the female gamete may be much larger than the male one (sperm), the latter fertilizing the egg which later produces oospores. Parthenogenesis is frequently present among fungi.

Mycoses.—Diseases caused by fungi are known as mycoses. The terminology of the mycoses varies considerably with different authors, but fairly well recognized terms are the dermatomycoses, or ringworm affections, otomycoses, onychomycoses, and maduromycoses. Again, the name of the affection may be taken from the fungus concerned in the cause, as sporotrichosis, blastomycosis, actinomycosis, or aspergillosis. However, there is also frequently great divergency of opinion in such classification. Thus Brumpt (1936), under the term "Blastomycoses," includes only the diseases produced by the budding fungi, (*Saccharomyces*, *Mycotorula* and *Torula*), or those presenting the form of yeasts (blastospores); and he definitely excludes the organisms produced by the non-budding fungi. However, many other authors include in this term diseases caused by fungi not only of the genus *Saccharomyces*, but of *Cryptococcus*, *Coccidiodes*, *Oidium* and *Monilia*. (*Candida*).

Pleomorphism.—The fungi frequently reveal remarkable variations in pure cultures and this is particularly found in the species which cause ringworm. Thus the morphology of the periphery of a dermatophyte may be entirely different from the original central inoculation growth, and the change may hold for subcultures from the peripheral

zone. Also, different spore forms may develop from the same culture. This is usually referred to as pleomorphism, but the term polymorphic is more applicable to many of these variations. It is well recognized that variations may result from culture environment—hence the necessity for standardization of composition, temperature and reaction of culture media used in research. (See p. 1192.) The term saltation has been employed to indicate variation in morphology in the fungus in different parts of the colony. Saltation should not be confused with mutation, as the two may not be identical.

Phycomycetes

The phycomycetes are sometimes referred to as Lower Fungi, as they approach more the primitive forms. The Ascomycetes and Hyphomycetes are classified in the group of Higher Fungi. The Phycomycetes are not usually regarded as of great importance in human pathology. However, Brumpt and Ramsbottom have classified two important fungi, *Rhinosporidium seeberi* and *Coccidioides immitis*, under the Chitridiales, an order of Phycomycetes (see p. 1152). Here classified as Ascomycetes.

Otherwise it is only necessary to consider the Mucoraceae, which are moulds so often observed as cotton-like areas on decaying foodstuffs, or as Petri dish contaminants. The best known species is *Mucor mucedo*, so common on horse dung, but it is now denied that this fungus plays any part in human mycoses, although a case of mucor keratomycosis has been reported, where this common mould was isolated from a corneal lesion.

Absidia corymbifera (Mucor corymbifera).—The sporangium of this fungus averages from 50 to 70μ in diameter, with smaller ones from 10 to 20μ. The spores are spherical and measure from 3 to 4μ in diameter. It grows well on Sabouraud's medium. This species has been reported in a number of instances as the cause of nasal, pulmonary and auricular mycoses (Brumpt 1936).

Rhizopus.—Two species of this genus, *R. niger* and *R. parasiticus*, have been regarded as possibly pathogenic. The former was isolated from rare cases of "black tongue," and the latter from the sputum of a case diagnosed as pulmonary mycosis. Vuillemin and others doubt the relationship to black tongue which is now regarded as a symptom of a vitamin deficiency. The columella of *R. niger*, after the dehiscence of the sporangium, is mushroom shaped. The sporangia, when mature, have a black color.

Ascomycetes

Among the Higher Fungi are included the classes Ascomycetes and Fungi Imperfecti. The Ascomycetes are probably the most definitely characterized of the fungi, this class having a special type of sporangium called an ascus (little sac). In the young ascus there is a single nucleus, which by 3 successive divisions frequently results in 8 uninucleated ascospores. However, in some forms only 2 or 4 ascospores may result—or even 16 may occur.

The yeasts which reproduce typically by budding, but produce ascospores, are included in this class. Other budding forms may fail to show ascospore formation (asporogenous yeasts). In some Ascomycetes there is a well developed thallus, with septate hyphae (the hyphae of Phycomycetes are non-septate). In the yeasts only a sprout mycelium is known.

Piedra (Trichosporosis).—This is a fungus disease of the hairs, in which small nodules form along the shaft. They are about the size of the nits of head lice, but more or less surround the hair instead of projecting off at an angle as do the ovoid lice nits. The small, sandy, concretions are black in color and very hard, hence the name piedra—stone. The disease was observed frequently in Colombia in women and the infection was thought to be due to the application of a mucilaginous preparation to their hair. It also occurs upon the hair of the beard. The stone-like concretions are caused frequently by the species *Piedraia columbiana*

(*Trichosporum giganteum*). Another species has been reported from British Guiana and from Brazil, *P. hortai.* and Souchard 1937 has found this species in cases in Cochin China. Horta has published an excellent monograph regarding the condition. If an infected hair is examined in liquor potassae, the nodule will be found to be made up of facetted bodies matted to the side of or, at times, encircling the hair, but not invading it. The fungus grows on Sabouraud's medium but better on carrot. A form of *Trichonocardiasis* similar to piedra has been reported by Chalmers and caused by a species of *Nocardia* (actinomyces). Infections involving either the hairs of the head or bearded regions have a wide distribution,

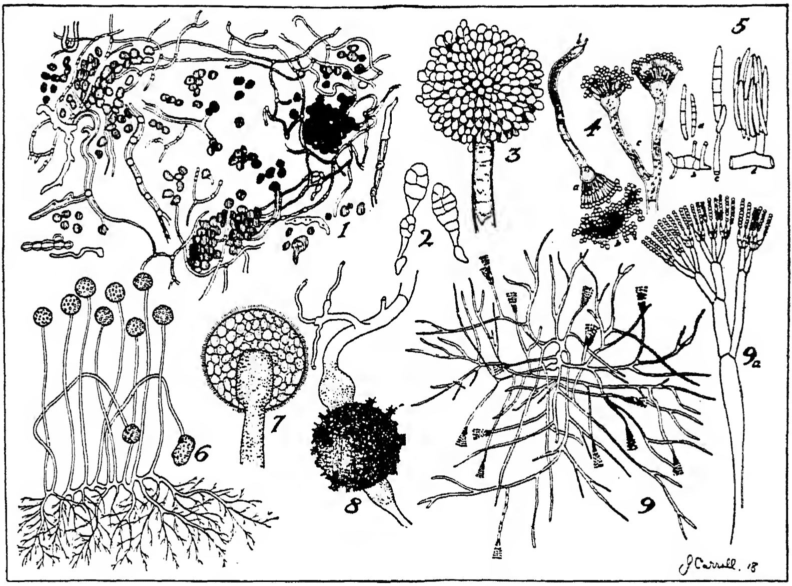


FIG. 247.—1, Tinea versicolor scrapings (*Malassezia furfur*). 2, *Alternaria*. 3, and 4, *Aspergillus*. 5, *Fusarium*. 6, 7, 8, *Mucor*. 9, 9*a*. *Penicillium*.

according to MacLeod. Lampe (1940) reports that piedra with black nodules caused by Piedraia is frequently met with in the native population of Batavia.

Manson-Bahr (1940) also emphasizes that trichosporosis must not be confounded with *Trichomycosis nodosa* (Trichonocardiasis) which is a fungus disease of the hair, and common enough on the axillary, scrotal, and face hair in Europe and elsewhere. Also, it should not be confounded with *trichorexis nodosa*, a non-parasitic disease of the hair shaft, which is split up at different points into brush-like bundles of fibres and is thus easily fractured. It should also not be confused with moniliform hair another non-parasitic condition which is congenital and hereditary.

Tricomycosis has been reported in Central Africa and Asia and Japan, as well as in Europe. Casals (1939) has reported cases of trichonocardiasis in Cuba. In some respects the condition resembles piedra. The shafts of the hairs, especially those of the axilla, are said to be attacked. The

species studied by Vuillemin was named *Trichosporon biegeli.* The fungus may be easily cultivated by inoculating the nodosities on Sabouraud's medium. In culture mycelial growth occurs composed of arthrospores giving rise to blastospores, and in older cultures to ascospores. Cases have been reported in which the beard and mustache have also been attacked and in which they were matted together so that they could not be combed. Manson-Bahr reported a case in which the hairs in the affected part had a beaded and nodular appearance and the hair emitted a peculiar odor. Microscopically, the polygonal cells were yellowish green or brown in color. The infection may extend to the skin and cause a severe intertrigo.

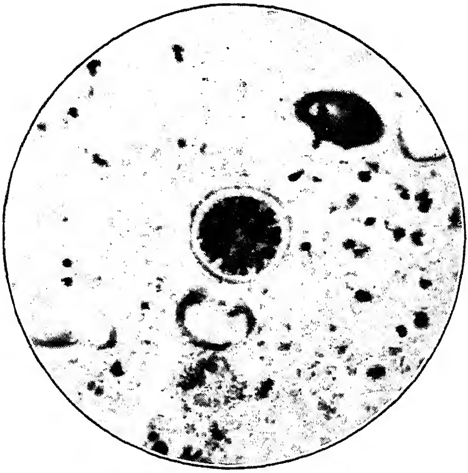


FIG. 248.—*Coccidioides immitis.* Endogenous sporulation in center. (Courtesy of Commander H. E. Ragle, Medical Corps, U. S. Navy.)

Treatment.—Sutton and Sutton (1939) recommend that the hair should first be sponged with benzine to remove all the gritty particles. Chalmers reported excellent results by applying to the affected hairs a 2 per cent formalin solution in alcohol. At night, a 2 per cent ointment of sulphur was applied. A 5 per cent alcoholic solution of salicylic acid has also been recommended. Manson-Bahr has also obtained success with a similar form of treatment.

Coccidioidal Granuloma (Coccidiomycosis).—The disease may occur with verrucous or ulcerative lesions of the skin sometimes with involvement of the bones, joints and viscera. The first case, affecting a Brazilian soldier, was reported from Argentina in 1892 by Wernicke. Later his assistant, Posadas, made thorough studies of the parasite, including animal inoculations. Posadas first regarded the parasite as a Coccidium. The name *Coccidioides immitis* was later given it by Rixford and Gilchrist and the parasite was shown to be a fungus. The first reported case resembled clinically mycosis fungoides. In tissues, more or less round cyst-like structures occur, varying from 4 to 80μ in diameter, containing

endospores and having a thick, doubly contoured capsule. These rounded elements never show budding in tissues. Cultures of the organism on artificial media develop, creamy white colonies appearing in 4 to 17 days on malt extract agar, later becoming cottony and brown with abundance of chlamydospores (4 to 7μ). The hyphae are about 3μ wide. MacNeal and Taylor have noted endospore formation in anaerobic cultures. Inoculation of monkeys, rabbits, guinea pigs and mice with cultures give rise to the same cyst-like structures, with endogenous spores, as noted in human tissues.

By the end of 1935, more than 400 cases of the affection had been reported, with 80 per cent of the cases in the United States from California, where the disease is reportable. Scattered cases occurred in other states. Dickson (1938) has reported upon valley fever or desert fever of the San Joaquim Valley as an acute coccidioidal infection. The lesions of the skin resembled erythema nodosum and there was usually pulmonary involvement. He thought that the infection was caused by inhalation of the chlamydospores. A great majority of the cases promptly recovered. Brumpt has described a species, *C. histosporocellularis*, as the cause in certain Brazilian cases, and Dodge notes the desirability of further comparison of the organisms found in Argentina and the United States. Coccidioidal granuloma has also been reported from Mexico, Uruguay and Argentine.

A form known as paracoccidioidal granuloma has been found especially in Brazil and in several other parts of South America. Several species of *Paracoccidioides* have been described as the cause. Moore (1938) has reported that a generalized form of the disease may be due either to the species *Paracoccidioides braziliensis* or to *P. tenuis*, and that a localized form involving the buccal mucosa is due to *P. cerebriformis*. Rosenfeld (1940) has found the species *braziliensis* to be the common one and Iriate (1940) has found this species in Caracas.

Moore has classified *Paracoccidioides* in his family *Coccidioideaceae*. Conant and Howell, (1941) who have compared a number of strains of blastomyces isolated in north America with a number of strains of *Paracoccidioides* isolated in South America, the source not given, find that they differ only slightly in cultural aspects and morphology and suggest the terminology of *Blastomyces dermatididis* and *Blastomyces braziliensis*, as they do not consider the differences of generic importance. Other mycologists retain the former in the genus *Coccidioides*.

Coccidiomycosis may start as a skin affection, or first may become manifest as a pulmonary lesion. From either atrium of infection generalization may follow. The skin lesions may be nodular, ulcerative, papillomatous, or verrucous. They often resemble those of tuberculosis, with the presence of cold abscesses. The fungi occur either isolated or in giant cells. It is this tendency to metastasis, through blood and lymph channels, that explains the seriousness of the disease. The differentiation from tuberculosis, syphilis, and other fungus infections is made by finding the non-budding cysts, with endospore formation. A wet preparation is entirely satisfactory for examination.

Complement fixation reactions with antigens prepared from cultures of the infecting organism have been obtained, but the reactions are not

sufficiently specific to be of diagnostic value. An allergic skin reaction has been described from the injection of such an antigen, but it is a question whether it is reliable. Kessel (1939) believes that active cases yield positive intradermal tests, but the question of greatest uncertainty has been with reference to possible cross-reactions in cases of tuberculosis. Hurwitz, Young and Eddie have reported positive coccidioidal reactions in patients having no known coccidioidal infection.

Smith (1941) has reported that he obtained a positive reaction to coccidioidin in 5 cases of coccidioidal granuloma, but no reaction to the antigen blastomycin. In one case of Gilchrist's disease, only a moderately positive reaction was obtained with blastomycin and no reaction with coccidioidin or sporotrichin. He thinks that coccidioidin is of value in confirming or denying the presence of the corresponding disease. However, Lewis (1941) points out that although coccidioidin appears to elicit specific reactions, it may be of limited diagnostic value in communities where the disease is endemic. Farness and Woolley demonstrated that 90 per cent of school children in a district in California in which coccidioidomycosis is prevalent all gave a positive reaction to coccidioidin, showing that the test there would be valueless. In New York, however, where coccidioidomycosis, according to Lewis, has not been reported, no positive reaction was obtained.

Kessel believes that the skin test can be used as an aid to diagnosis, but probably no more reliance should be placed on it than is usually given the tuberculin test. He thinks that tuberculosis patients usually give negative reactions. Nevertheless, further careful studies and confirmation of all this work is necessary before it can be regarded as conclusive. Very little is known as to the source of infection of coccidioidal granuloma but the great resistance of the cultural spores, and the occurrence of laboratory infections, has suggested the inhalation of dried spores as the mode of inoculation rather than cutaneous entrance from dirt of plant material (thorns or prickles). However, Stewart and Meyer have reported the isolation of the fungus from the soil.

It has been suggested that rodents may constitute a reservoir of *coccidioidomycosis*, and Ashburn and Emmons have found that of 105 rodents trapped in the desert around San Carlos, Arizona, 9 showed gross pulmonary lesions in 7 pocket mice (*Perognathus*), 1 kangaroo rat (*Dipodomys*) and 1 ground squirrel (*Citellus*). Microscopically, a total of 20 nodular lesions were found in the 7 mice and 1 rat. In all of the nodules the fungus cells were present either in small or in large numbers.

Stiles and Davis (1942) report an increase in infection of the lower animals not only in wild rodents but dogs, cattle and sheep.

The outlook is generally unfavorable in the generalized form of the disease and death usually occurs within 3 or 4 years. Of 24 cases collected by MacNeal and Taylor, only 2 recovered. A few patients have recovered following drainage or excision of local lesions.

Treatment is generally unsatisfactory, but large doses of potassium iodide, 20–30 grains 3 times a day, well diluted, have sometimes been found valuable. X-ray treatment has been recommended for the local lesions; also the injection of a 1:1000 solution of potassium iodide. A few cases have been treated with sulfanilamide but the results have not been encouraging. In one case with a cerebral lesion death occurred after two months treatment with sulfanilamide, Storts (1939).

Rhinosporidiosis.—This is a polypoid affection, chiefly involving the mucous membranes of the nose, but also invading the ears, the lacrymal sac, the uvula and more rarely the mucosa of the penis.

Dhayagude (1941) has described a case in a Hindu in which the parasite was found in nodules scattered over the body and there was no nasal or nasalpharyngeal growth.

It is caused by a fungus, *Rhinosporidium seeberi*, which was first reported by Seeber in 1896 in Argentina.

It was considered as a coccidial parasite, but the work of Ashworth (1922) proved it to be a fungus and not a protozoon. The organism is found within soft, very vascular, raspberry-like tumor masses, which are difficult to remove completely by reason of their friability and tendency to bleed profusely. The youngest forms measure 6μ and the largest ripe sporangia 300μ in diameter; they have a thick wall and contain thousands of nucleated spores. The infection has been reported from India, Cochin China, Uruguay, Argentina and the United States. The mode of transmission is unknown, but spores and ripe sporangia may be found in the nasal mucus.

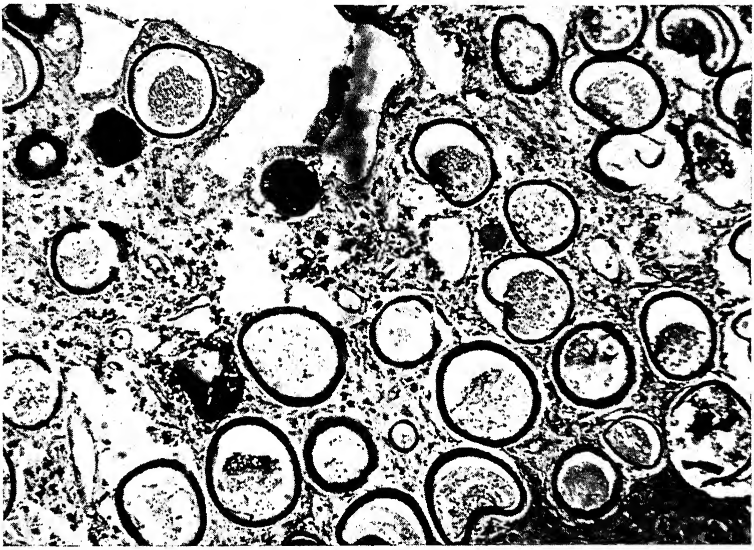


FIG. 249.—*Rhinosporidium seeberi*. Section from a nasal polyp. (U. S. Naval Medical School.)

Apparently a closely related organism, *R. equi*, has been found in nasal cavities of the horse in South Africa.

The course of the disease is a long one and there is a marked tendency for it to recur.

Satisfactory cultivation of the parasite has apparently not been obtained and the inoculation of animals has not resulted successfully.

Treatment.—The most satisfactory treatment has been found to be the removal of the polypi from the nostrils by means of the wire snare. Wright reported that the tumors disappeared after intravenous injections of tartar emetic.

Blastocystis hominis.—Ramsbottom considers this non-pathogenic fungus as belonging (morphologically) to the same group as Rhinosporidium. Blastocysts are frequently found in stool examinations and may be mistaken for amoebae or other protozoa.

They are particularly abundant where the amoeba, *Dientamoeba fragilis* is found (symbiosis?). *B. hominis* is a parasite of the large intestine. It is a frequent contaminant of cultures made in examinations for amoebae. Brumpt reports this fungus found in 50 per cent of a series of stool examinations. It varies from 3 to 15μ in diameter and has a large central vacuole, which does not stain dark brown as does the glycogen mass of *Iodamoeba*. The protoplasm surrounding the vacuole varies in thickness in different sections of the ring and shows a varying number of nuclei. Budding forms may be seen.

Blastomycosis.—Blastomycosis of the American type, or Gilchrist's disease, is characterized by granulomatous and suppurative processes of the skin and subcutaneous tissues and sometimes of the lungs and other internal organs. Most of the cases first discovered in the United States were in the region of Chicago, but later, they have been reported from many parts of this country. Marlin and Smith (1939) write that cases have been found in at least 28 states. They have also been reported in Canada, Puerto Rico, Cuba, South America, and Europe. The cases have been more numerous in males than in females. The blastomyces have been found, especially in the pus from the lesions and sometimes in the sputum.

Gilchrist, in 1896, described the organism causing human blastomycetic dermatitis as encapsulated and budding in tissues, with mycelial forms in cultures. Dodge has classified this yeast-like fungus in the genus *Zymonema, Z. dermatitidis* (usually however classified as *Blastomyces dermatitidis*). Other species have also been reported in blastomycosis, as *Cryptococcus gilchristi*, and *Cryptococcus hominis* (Vuillemin) in Europe.

In tissues, there are found spherical or ovoid cells singly or in groups, varying from 7 to 20μ in diameter. Budding forms are common, and the thick, highly refractile membrane makes the cells appear as double contoured. In cultures of *Blastomyces dermatiditis*, on solid media, there appears about the third day a small, creamy, prickled (coremia) colony which shows hyphae about 3μ in diameter. Chlamydospores (7 to 8.5μ) may be terminal or intercalary. The ascus in 8-spored. No pellicle is formed on sugar broth. The guinea pig is susceptible to infection but the mouse is more susceptible and may be inoculated either intraperitoneally or intratesticularly. The infection is fully developed in the laboratory animal by the third week, yeast-like bodies being present in the tissue nodules.

The disease may start as a skin lesion or this may be secondary to a primary pulmonary invasion. The skin lesions may resemble a verrucose tuberculid, a syphilitic gumma, or a sporotrichosis lesion. The exact diagnosis depends upon laboratory tests. In generalized blastomycosis the lung is involved in more than 90 per cent of the cases, and in skin blastomycosis it is secondarily invaded in about one-third of such cases. In primary pulmonary blastomycosis a bronchopneumonia occurs from which the infection may generalize. There is less tendency to cavitation than in phthisis. The sputum is apt to be blood stained and may contain the fungus. Next to the lungs and skin, the infection most frequently invades the kidneys, but the organism is not apt to be found in the urine unless there is invasion of the bladder or prostate. Bone and central nervous system involvement more rarely occur.

Martin and Smith (1939), who have analyzed the reports of 340 cases including 13 of their own, recognize 2 clinical types of infection: (1) a cutaneous one which proceeds as a chronic or subacute ulcerative process and which usually responds to treatment with iodides or radiation; and (2) a systemic form, a highly fatal disease, characterized by pulmonary infection and wide spread distribution of lesions. Antibodies were found in the sera of some patients who were heavily infected. See p. 1194.

Prognosis.—If the infection is of the cutaneous type and does not become systemic, the outlook is usually good. In cases with generalized infection and pulmonary involvement, the prognosis is unfavorable and the disease highly fatal.

Martin and Smith (1939) found that in severe cases a hypersensitiveness to the fungus develops which can be estimated by cutaneous tests,

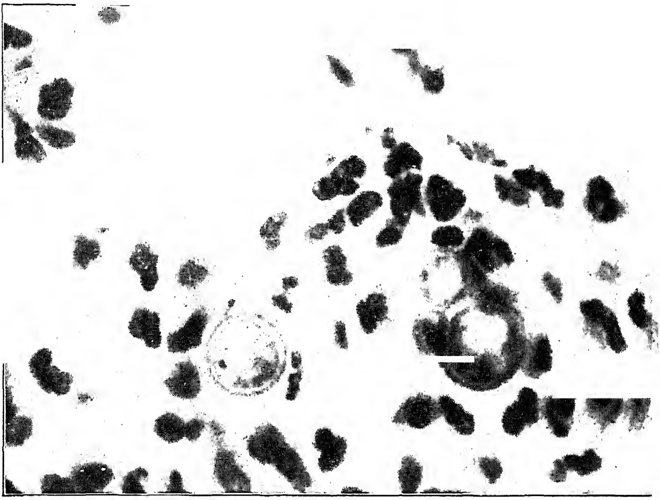


FIG. 250.—*Z. dermatitidis* (*C. gilchristi*). Doubly contoured organisms found in oidiomycosis (blastomycosis). (From Buschke after Hyde and Montgomery.)

and they think it can be reduced by repeated injections of heat killed vaccines. They think it is dangerous to treat cases that are allergic to the fungus with potassium iodide and recommend treatment first with vaccine.

Treatment.—Lord (1936) lays stress on the improvement of the general nutrition and the administration of potassium iodide. The local cutaneous lesions usually respond to treatment with iodides or radiation. The local lesions may be in some cases advantageously excised, or aspirated, drained and irrigated with 1 per cent copper sulphate solution or with iodine.

Bush (1941) has reported upon the treatment of a chronic generalized case of blastomycosis in which curative result was obtained with iodides and radiation with the Roentgen ray. However, large daily doses were necessary, as 360 grains (23 gm.) daily. The drug was given intravenously

as the compound solution of iodine U.S.P. with admixture of sodium thiosulphate, and Bush reports this was a convenient, safe and efficient method for administering iodides. The thiosulphate is added to prevent sclerosis of the veins.

Meningoencephalitis.—Dodge and Ayers isolated a fungus from the surface of the, medulla in a case diagnosed as meningoencephalitis. The name given this parasite

FIG. 251.—Blastomycosis, case of Dr. J. B. Bush, Alabama. (Courtesy Arch. Dermat. & Syph.)

was *Zymonema capsulatum*. In the lesions, only budding cells were found. In cultures, thin-walled hyphae (3.5 to 4μ) were noted. Chalmydospores developed from racquet mycelium. The relationship of the organism to *Histoplasma* is not clear. (See below.)

Lymphangitis epizootica has been recognized as a fungus infection, especially of the cutaneous lymphatics of the horse, since 1883, when Rivolta described *Cryptococcus farciminosus* as a cause of the disturbance. The lesions, which consist of nodules, and ulcerations of the skin in situations rich in lymphatics, are frequently found where irritation from rubbing of the harness may result. The disease extends through the lymphatics and is a chronic one. It has been observed especially in Asia and more recently in southern and western Europe and northern Africa. It was studied by Tokishige in Japan in 1896 and in the Philippines in 1902 by the writer, in an outbreak resembling farcy. Four years later a case

of human infection with cutaneous lymphatic lesions of chest wall, due apparently to this same organism, was observed in Manila and cultures of the *Cryptococcus* obtained.

Although the patient was only seen on two occasions, there was no evidence of visceral involvement and general infection and the lesion healed in several months after complete excision and curettage. The organism was definitely identified as a fungus (Torula). However, for a long time it was described by a number of other investigators as a species of protozoa. Other cases of human infection with it have also been reported by Brault, Negre and Bridre and Ziemann. In Negre and Bridre's case, a cutaneous lesion resulted first in an abscess on the right hand. After excision,

FIG. 252.—Camera lucida drawing of culture of *Cryptococcus farciminosus*.

the wound healed, but later a number of other small abscesses occurred in the region of the wrist, which also healed after incision. Shortly afterwards there appeared induration of the lymph vessels along the upper border of the radius. This disappeared several weeks later. However, later suppuration occurred in the scar. The patient was then treated with injections of 606 intravenously and completely recovered. Brumpt (1936) and Dodge (1935) mention that instances of human infection with the parasite may occur in individuals who care for infected animals and Stovall and Almon (1941) say that the fungus has been inoculated into man. The parasite, however, appears to show no great virulence in human beings and there have been no reports of visceral involvement from it. Man is probably only an accidental host. Nino in Argentina has reported an ulcerated condition of the face from which a generalized infection resulted with a species named *Cryptococcus pschrophylicus*. The organism was easily cultivated at 22-25°C. and guinea pigs, white mice and rats were successfully inoculated.

Histoplasmosis. *Histoplasma capsulatum.*—Darling, in 1906, reported in Panama 3 cases of fatal human infection caused by an organism described as *Histoplasma capsulatum.* The disease resembled in many respects kala-azar, and was accompanied by splenomegaly and leukopenia. The organism was first regarded as a protozoan. Rocha-Lima, in 1912, suggested it was identical with *Cryptococcus farciminosus.*

Watson and Riley (1926) reported the first case of infection in the United States. Subsequently 9 other infections were reported in this country, of which 8 were in adults. The ninth case, which was reported by Shaffer and his associates (1939), was in an 11 months old child, and the tenth case, of Amolsch and Wax (1939), was also in a child, of 8 months. Both cases were fatal and the organism was discovered in the spleen. Reid, Scherer and Irving (1940) have reported 2 cases in the

CASE NUMBER	REPORTED BY	STATE OR COUNTRY	AGE	SEX	RACE	DISTRIBUTION OF PARASITES LIMITED TO						
						Generalized	Skin	Naso-oral cavity	Lungs	Lymph nodes	Adrenals	Other
1	Darling	Canal Zone	27	M	Negro	+						
2	Darling	Canal Zone	29	M	Negro	+						
3	Darling	Canal Zone	55	M	Chinese	+						
4	Strong	Philippines	35	F	Philipp.		+					
5	Watson, Riley	Minnesota	52	F	White	+						
6	Phelps, Mallory	Honduras	24	M	Hondur.				+			
7	Wade	Philippines	40	M	Philipp.	+						
8	Crumrine, Kessel	California	42	M	Negro	+						
9	Müller	Java	7	M	Javanese	+						
10	Dodd, Tompkins, De-Monbreun	Tennessee	6 mo.	M	White	+						
11	Hansmann, Schenken	Iowa	43	M	White		+	+	+	+	+	
12	Agress, Gray	Missouri	7 mo.	M	White	+						
13	Amolsch, Wax	Michigan	8 mo.	F	White	+?						
14	Schaffer, Shaul, Mitchell	Virginia	12 mo.	F	White	+						
15	Negroni	Argentina	?	?	?		+		+	+		
16	Clemens, Barnes	Kentucky	33	F	Negro	+						
17	Gunter, Lafferty	Alabama	54	F	White	+						
18	Humphrey 1	Michigan	17	M	White	+						
19	Humphrey 2	Michigan	46	M	White	+						
20	Williams, Cromartie	Tennessee	56	M	White			+		+		
21	Parsons 1	Michigan	67	M	White						+	
22	Weller	Ohio	12	M	White ?	+?						
23	Parsons 2	Michigan	25	F	White	?		+				
24	Forry, Culbertson	Indiana	10	M	White	+						
25	Martin, Silber	California	43	F	White				+		+	Liver
26	Currie	Indiana	62	M	White						+	
27	Vilella, Pará	Brazil	3	F	Mulatto	+?						
28	Meleney 1	Tennessee	50	M	White				+			
29	Meleney 2	Tennessee	69	M	White				+			Liver? Spleen?
30	Blache, Moore	Missouri	33	M	Negro				+			Prostate
31	Reid, Scherer, Irving	Virginia	38	M	Negro	+						
32	Mantell, Troy	Florida	42	M	White	+						

Summary of human cases of histoplasmosis showing distribution of the parasites. (After Meleney.)

United States in which they emphasize the enormous number of parasites seen in bone marrow preparations, and they suggest sternal puncture studies for diagnosis. In one of their cases, the diagnosis was made before death.

Meleney (1940) has analyzed 32 cases of histoplasmosis, of which 24 have occurred in the United States. Thirteen of the cases which he reviews have not been published before. He points out that the macroscopic pathology has varied with the clinical manifestations. In most of the cases, gray or white nodules or extensive areas of necrosis have been found in one or more organs, and in the lungs abscess cavities or tuberculous cavities have been encountered. Caseation of the adrenals has been found in a number of cases, and in 3 the adrenals were the principal organs, or only organs, involved. Some cases have shown ulcers in the small or large intestine, either very superficial or deep. Nodules have also been found in the submucosa or deeper coats of the intestine. In a

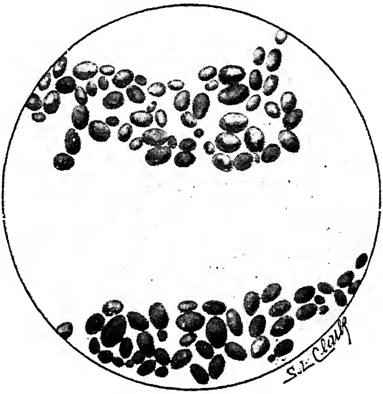


FIG. 253.—Yeast cells. *Saccharomyces cerevisiae.* (Coplin.)

few cases occurring in infants, there have been no macroscopic lesions suggesting local areas of necrosis, but the organisms have been discovered in the spleen. In a few instances, the lesions have been confined to the skin. The accompanying table of Meleney summarizes the distribution of the parasites. In some cases, the organisms have been limited to the necrotic areas. In other cases they have been found widely distributed in the organs of the body which are rich in reticuloendothelial cells.

He has since (1941) described two further cases which were of interest on account of the pulmonary features which before death had led to diagnosis of malignant disease and tuberculosis. The correct diagnosis was not made until after death when it was found that the lungs were involved in nodule formation with cavitation. Acid-fast bacilli were found in both cases but sections of the lesions revealed endothelial cells packed with the causative organism.

Derry (1942) and his associates have reported the first case from England. Post-mortem examination revealed a large mass behind the

liver with necrotic areas containing the yeast cells. The organism was identified by cultures as *Histoplasma capsulatum*.

Henderson, Pinkerton and Moore report a case in a man 70 years of age in which there was ulcerative enteritis, a condition which has been referred to by Meleney in the analysis of other cases.

DeMonbreun and Anderson (1939) reported an infection in a bull-terrier in Tennessee, the organism being demonstrated in cultures of the blood before death and in the postmortem examination.

The infection was transmitted to young dogs, both parenterally and by mouth, both with material from the original dog and by the inoculation of cultures. Experimental infections have also been reported in monkeys and mice. Hansmann and Schenken (1933) have reported the infection of guinea pigs, rabbits, dogs and rats with a species which they named *Histoplasma pyriforme*. Niño in Argentina has described a Cryptococcus which caused a generalized infection originating from an ulcerated condition of the face. The organism was cultivated best at a temperature of 22–25°C. but no growth was obtained at 37°C. Guinea pigs, white mice and rats were successfully inoculated. Negroni (1938) has reported a case from the Argentine. Villela (1941) has reported the first case in Brazil which was in a child and which resulted fatally. In this case there was diarrhoea with blood in the faeces and progressive emaciation.

Cifferi and Redaelli believe that Histoplasma may be the cause of a form of dermatitis exfoliativa associated with lymphadenitis. The fungus cells were found within phagocytes in the enlarged lymphatic glands.

Brumpt (1936) classifies *Cryptococcus farciminosus* in the same genus, *Histoplasma*, together with *Histoplasma capsulatum*. On the other hand, Dodge has classified *Cryptococcus farciminosus* under the genus *Zymonema*. If one compares the cultures of these two organisms, their differentiation is clear. *Cryptococcus farciminosus* never produces mycelium in cultures and of the type which *Histoplasma capsulatum* does. Benham has recommended the term *Cryptococcus hominis* for organisms of the latter type.

Conant (1941) has made a cultural study of the life-cycle of *Histoplasma capsulatum* and believes the fungus should be placed in the Moniliacea of the Fungi Imperfecti.

It is not clear just what the relationship of the fungus, which de Monbreum has isolated from the dog is to *H. farciminosus*. His illustration of cultures of the dog species suggest it is a different one.

Diagnosis: Many of the cases show irregular fever, emaciation, splenomegaly, leukopenia and anaemia. Diagnosis by biopsy and the demonstration of the organism by microscopical examination or by cultures of it, are methods of choice when lesions are accessible. Zarafonetis and Lindberg have suggested that intradermal skin tests might be employed for diagnosis in which a filtrate of a culture of the fungus was used as an antigen.

The prognosis is generally unfavorable when the fungus has become widely disseminated. Only a few cases of recovery have occurred.

TREATMENT.—When the primary lesion occurs in the skin, the infection may sometimes be prevented from extending by early excision and curretting. Negre and Bridre found that incision of the abscesses did not result in complete cure until 606 (salvarsan) was administered. In a case treated by Clemens and Barnes (1940) in which the primary lesion was possibly an ulcer on the face, this was healed after treatment with bismuth. However, this patient was also a syphilitic and the parasite was recovered from lymph nodes after death. In one case reported by Meleney in which the cervical lymph nodes showed the organisms, the patient recovered after treatment with neostam, a pentavalent antimony preparation. Meleney believes that antimony preparations such as potassium antimony tartrate, the trivalent organic preparations such as fouadin, and the pentavalent preparations such as neostam should receive particular attention in therapy.

THE MONILIASES

There is a large group of fungus infections which have been attributed to various yeast-like organisms, many of which show mycelial development

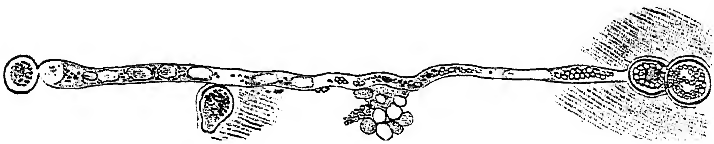


FIG. 254.—*Endomyces vuillemini.* Mycelial thread with four ripe chlamydospores and conidia in the middle of the picture. (After Plaut.)

in cultures. The best known of these moniliases is "thrush," in which greyish-white membranous patches form on the mucous membrane of the gums, tongue, buccal cavity and pharynx, chiefly affecting marasmic infants or feeble old people. The fungus rarely attacks well nourished individuals.

On examination of a fragment of such membrane, we find yeastlike bodies which, when cultured, tend to show a yeast morphology on solid media and a mycelial one in liquids.

In stab cultures of agar or gelatin there are found yeast-like forms on the surface, but lower down on the stab (partial oxygen tension) we have an outgrowth of mycelial threads showing budding. The addition of extract of carrots to the standard media promotes mycelial formation.

Although the generally accepted name for this fungus is *Monilia albicans* (the name *Oidium albicans* was given at an earlier date—1853), this "albicans" species has been assigned by different authors to many other genera, of which might be mentioned *Saccharomyces*, *Mycoderma*, *Endomyces*, *Mycotorula*, and *Dematium*. Henrici has prepared a table which gives a simple differentiation of the yeast-like organisms often referred to in moniliasis literature. In *Endomyces* there are both mycelium and budding cells, the mycelium forming asci by fusion of contiguous cells. Losing the power to form ascospores, the fungus becomes a *Monilia*. Should a *Monilia* lose the power to

form mycelium, it becomes *Cryptococcus* (an asporogenous yeast). When *Endomyces* loses the power to form mycelium, it becomes *Saccharomyces*, a true yeast, which never forms mycelium and reproduces by budding and the formation of ascospores (resulting from the conjugation of adjacent cells or by parthenogenesis). The false yeasts (*Cryptococcus*) reproduce by budding, but do not form mycelium or ascospores. Castellani, who places chief reliance on fermentation reactions in classification and gives little attention to morphology, presented an elaborate separation of species concerned in the various moniliases. It is astonishing how many species are described in the literature based on a single cutaneous, pharyngeal or pulmonary condition from which yeast-like bodies were noted. Competent mycologists have in recent years stressed cultural studies with various media as is required for bacteria, along with determination of pathogenicity. Dodge has grouped the more important of these "monilia" parasites in the genera *Castellania* and *Syringospora*. However Burt and Ketchum (1941) now regard the genus *Monilia* as identical with *Candida*.

Clinical Types.—(1) Besides "thrush" and "perleche" (mycosis of the angle of the mouth of young children, with macerated whitish areas) we have moniliases of the perineal or inguinal regions of infants, particularly those poorly nourished. Probably many of these "monilias" are saprophytic and only develop in individuals of lowered resistance. Yeasts are very common findings in the stools of normal individuals and these may find a suitable soil in cachectic children in regions adjacent to the anus. Some of the so-called body eczemas and dysidroses of hands and feet are associated with "monilias." Many cases of "athletes foot," particularly where the toes are closely approximated, belong to the moniliases, although by far the greater number of such cases belong to the ringworm group.

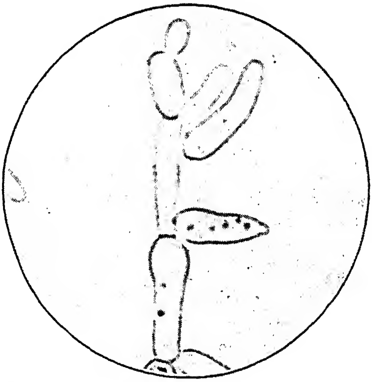


FIG. 255.—Thrush fungus. (Kolle and Wassermann.)

Dodge points out that species of *Monilia* are predominantly saprophytic. Of 53 species referred to the genus *Castellania* by him, there may be noted *Castellania tropicalis* and *C. pulmonalis*, both of which were connected with pulmonary conditions incident to inspection of tea dust, inhaled by experts grading teas. Many of the species listed by Dodge are based on a single case, and many of them fail to show any pathogenicity (and are apparently saprophytes).

In the genus *Syringospora*, he classifies the species *albicans*, the classical fungus of thrush, referred to above. In this same genus is classified *Syringospora psilosis* (*Monilia psilosis*), which was regarded by Ashford for a number of years as the cause of sprue. This disease, however, is now recognized as a deficiency disease closely related to pernicious anaemia.

Stitt (1938) emphasizes the care that one should take in describing as the etiological factor, yeast-like bodies which may be casually found in inflammatory lesions of the skin or in the sputum or faeces, unless they are demonstrated to be pathogenic species. He points out that in many cases it must be kept in mind that many skin lesions supposed to be due to fungi are really bacterial (staphylococcal, streptococcal, and even due to the colon bacillus); that cases resembling cutaneous blastomycoses and sporotrichoses have been found to show "monilia" forms of fungi; and in cases resembling

chronic bronchitis or pulmonary tuberculosis a great number of "monilia" species have been reported. Vaginal discharges may also be due to species of "monilia," as well as to *Trichomonas vaginalis*.

Torulosis.—Another ill-defined group of yeast-like fungi with pathogenic properties are those listed in the genus *Torula*, in which the organisms reproduce only by budding, do not produce mycelium or endospores, and do not ferment carbohydrates. They rarely if ever cause lesions of the skin, but appear to have definite affinities for the tissues of the central nervous system and the lungs, though they may produce destructive granulomatous lesions in other organs of the body. The respiratory tract is regarded as the probable portal of entry.

Freeman (1931) collected a number of cases of central nervous system involvement, which suggested neoplasm or encephalitis, but were associated with the presence of yeast-like organisms, *Torula histolytica*.

Dodge has called this organism *Cryptococcus histolyticus*. *Cryptococcus histolyticus* reproduces only by budding, the yeast-like cells averaging 3 to 4μ in diameter. The whitish to yellowish colonies on glucose agar appear heaped up, smooth, pasty, shining and thick. They do not cause fermentation, pellicle formation, or liquefaction of gelatin. The atrium of infection is probably pulmonary. The brain lesions consist of tubercle-like formations and the lungs often show the same appearance. Skin involvement is questionable. In a case reported by Harrison (1928), from a cystic blastomycosis of the cerebral grey matter, the organism liquefied gelatin after 26 days. Dodge has named it *C. meningitidis*.

The involvement of the cerebrum and meninges in torulosis suggests a brain tumor, particularly because of the eye symptoms, such as choked disc. A diagnosis may be possible by finding the yeast-like organisms in the cerebro-spinal fluid. Brumpt places the fungus of torulosis in the genus *Torulopsis* (*T. histolytica*). Stoddard and Cutler, Hirsch and Coleman, Massee and Rooney and others have reported further cases in the United States. The prognosis is usually unfavorable. The treatment has been unsatisfactory and the infection can only be treated symptomatically.

The genera *Cryptococcus* and *Malassezia* are often placed in the group Saccharomycetaceae Imperfectae (perfect stage unknown). As regards *Malassezia*, Dodge states that it is uncertain whether this genus belongs with the yeasts or the dermatophytes. As the very common skin lesion, pityriasis versicolor, is generally grouped with the dermatophytes, it would seem more convenient to deal with *Malassezia* under that grouping.

Fungi Imperfecti (Hyphomycetes)

Saccardo classifies under Fungi Imperfecti 3 main groups, Sphaeropsideae, Melanconieae and Hyphomycetes, but of these only the Hyphomycetes are involved in human pathology. Very confusing is the fact that in this class of fungi various workers have assigned to different stages of the same fungus different generic and specific names and another difficulty is that in the Hyphomycetes the complete life cycle is not entirely known.

Pityriasis Versicolor (Tinea Versicolor).—This very common skin affection is characterized by dirty yellowish-brown spots occurring upon

covered parts of the body, especially under the clavicles. These spots are sometimes referred to as "liver spots." The plaques are not elevated and do not show inflammation. A vigorous sweep of the thumb nail superficially across the patch (a sterile instrument is preferable) does not bring blood (*Signe du coup d'ongle*). The scrapings provide material showing an abundance of mycelium and spores of *Malassezia furfur*. The hyphae are from 2 to 3μ in diameter and the spores from 3 to 8μ. The spores are very refractile and may show budding.

On glycerin agar tiny white drops appear after a week. On Sabouraud's medium, the primary growth is exceedingly slow; months may elapse before a colony the size of a rice grain is formed. Castellani insists that the species found in tropical countries is *Malassezia tropica*, giving rise to *Tinea flava*. He also described in Ceylon a form of *Pityriasis nigra* which gave rise to black spots upon the skin, and from which he reported the isolation of the species *Cladosporium mansoni*.

Treatment.—The skin should be thoroughly cleansed daily by scrubbing with tincture of green soap and then sponged with a saturated aqueous solution of sodium thiosulphate. Further treatment for severe infections may consist of daily applications of Ung. hydrag. ammoniat., dram 1 to the ounce. Such treatment is satisfactorily effective. The undergarment should be sterilized to prevent re-infection.

Erythrasma.—This is sometimes confused with pityriasis but is a distinct skin affection which is caused by *Actinomyces minutissimus* (*Microsporon minutissimum*). The mycelium averages 1μ in diameter, often fragmented into bacillary arthrospores. Cultures are usually negative. Erythrasma spots are dark red to brownish (usually in the groin region or axilla). It is often confused with trichophytosis or lichen, as well as with tinea versicolor. The treatment is similar to that for pityriasis.

The Ringworm Skin Affections (Tinea)

Definition.—Contagious infections of the skin, hair or nails produced by various fungi. These dermatomycoses may vary greatly clinically, even as regards ring formation, but are grouped together because they tend to involve only the epidermis. The chief parasitic fungi invading the superficial skin layers belong to the family Trichophytoneae.

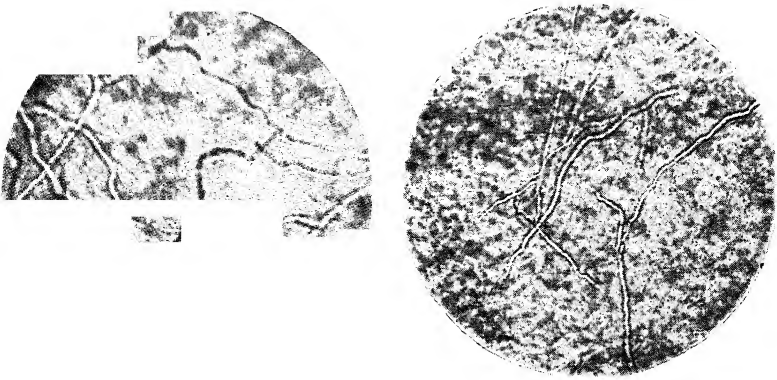
Dodge classifies these dermatophytes as, probably, imperfect stages of Gymnoascaceae. Sabouraud's classification of these fungi, here accepted, is based on both clinical and mycological grounds, and has been the guide of most dermatologists for the past 40 years, notwithstanding numerous valuable studies and classifications made by Castellani and Chalmers (1919), Vuillemin (1925), Langeron and Milochevitch (1930) and others.

The ringworms involving both scalp and glabrous skin are classified as the endothrix group, the ectothrix group, the microsporum group and favus.

The Endothrix Group.—It is usual to divide this group into an endothrix and a neo-endothrix group. In the former, the hyphae are confined to the interior of the hair, while in the latter, in addition to hyphae in the interior, we have a few hyphae growing along the outside of the hair, Arthur Whitfield notes that early in the invasion of the hair we find the

fungus in the root sheath as well as within the hair, but the external ones soon die out, leaving only the hair invasion. In the so-called neo-endothrix infections, the invasion of the root sheath continues for a longer period.

In the Malmstenia subtype of ringworm of the scalp (*Trichophyton tonsurans*), we have many normal hairs in the area of alopecia, and the diseased hairs project from 2 to 4 mm. above the scalp surface. The scales covering the affected spot, if gently removed, show flattened, diseased hairs lying beneath them, often assuming bizarre shapes. This infection rarely itches. It is a disease of young children and disappears at puberty—it has been suggested that gonadal activity explains the age exemption. It is very contagious. The quadrangular cells of the hyphae (often called spores) are 4 to 5μ long. A powdery, crateriform growth results on Sabouraud's medium. Guinea pigs can be



High Power Low Power

FIG. 256.—*Epidermophyton floccosum*, from skin scrapings. (Low and high power.)

infected. This ringworm also occurs on the face, neck and hands of children showing the infection as red areas with little vesicles or papules. It has been reported occasionally from cases of otomycosis and onychomycosis.

The Sabouraudia subtype is caused by *Trichophyton sabouraudi* (*T. acuminatum*) and is quite common in western Europe but of less frequency than the Malmstenia *Tinea tonsurans*. The hairs break off close to the scaly scalp patches, and show as black dots on the scalp surface. It may cause a trichophytosis of the hands and, secondarily, of the nails. It may invade the beard. The aleurospores are from 5 to 7μ in diameter and very fragile. Cultures are rather cupola-like.

The Ectothrix Group.—In this group mycelium is found both within the hair shaft and in the root sheath surrounding the hair. The designation "endo-ectothrix" has also been used for the ectothrix group. Sabouraud separates a megalospore and a microides subtype. The chief species of the large spore group is *Megatrichophyton roseum*, which is rather common in the north of England, where its spread seems to be through the barber shops, rather than from contact with animals. It has spread rather widely since the war, being reported from France, Germany, and in the United States, particularly Philadelphia.

The lesions are of the skin or of hair follicles, but chiefly of the beard, and are rather dry, showing no tendency to suppuration.

In the "microides" group, the common fungus is *Ectotrichophyton mentagrophytes* (*Trichophyton gypseum* var. *asteroides*). In sycosis vulgaris ("barber's itch") the lesions consist of a folliculitis of the scalp or regions of the beard complicated by infection in addition with pyogenic cocci. The inflammation results in a suppuration of the follicles containing the dead hairs. This same fungus when it invades more deeply the tissues is probably the most common cause of "kerion," in which, on the glabrous skin, we have patches riddled with openings from which pus oozes on pressure. These patches are often on the backs of the hands or forearms, in addition to the scalp and occur frequently in those who work with horses. When on the face or scalp, the affected hairs can easily and painlessly be extracted from the root sheath; they are, however, quite brittle and may break off. Epilation of the infected hair shafts is indicated. On mounting in caustic potash solution we find strings of spores (5μ) on the hairs extracted from the periphery of the lesion, or in the pus. The sheath at the base has spores varying greatly in size (2 to 11μ). The "microides" spores of the sheath may be confused with the small spore sheath of *Microsporum audouini*, but the former are arranged in chains while the latter show masses of polyhedric spores, about 3μ in diameter. Sullon and Sullon (1939) recognize a deep chronic infection sometimes resulting in a granulomatous type of eruption.

The Microsporum Group.—These small spored ringworms of the scalp are the most common ones in France and the United States. It is customary to recognize a human type which is important only for the scalp, as the lesions which may appear on the glabrous skin of the neck are rather insignificant and come from scalp transfer. It does not invade the beard. The name of this fungus is *Microsporum audouini*. The areas of alopecia of this human type show greyish scales, covering an area with definitely outlined borders and covered with diseased hairs, broken off about 3 to 4 mm. from the scalp surface. The area never shows any normal hairs. On epilating one of these greyish stumps of hair we note a whitish collar of polyhedric spores (2 to 3μ), which never penetrate the shaft of the hair. The spores of other common types of scalp ringworm tend to be larger (5 to 7μ). This infection attacks young children almost exclusively, and Brumpt advises us to think of an animal origin when we find one of these small-spored ringworms in an adult. The human type rarely causes even superficial pustulation. Of course, this may occur from bacterial infection in scratching by the child. Castellani (1934) reported that the species *M. scolaceus* (Bodin) leads to permanent alopecia in Ceylon and China.

The animal species of *Microsporum* (*Sabouraudites*) which have been chiefly studied are those belonging to the horse, the dog and the cat. That of the dog, *M. canis* (*M. lanosum*), produces both tinea tonsurans and circinate herpes in both children and adults. The lesions are generally scaly and dry. The cultures grow more rapidly than those of the human type and they show more abundant fuseaux. The cat species (*M. felineum*) seems to prefer the glabrous skin, producing dry erythematous lesions, which may go on to pustulation. Some kerions are due to the cat ringworm. It grows very rapidly in cultures. It is common in England, but less so in the United States.

Favus.—This disease usually affects the scalp hairs, although invading the glabrous skin and nails. It is characterized by golden-yellow, cup-shaped crusts (scutela), which form about the hair follicle orifices. The scutulum is made up of tangled mycelium surrounding the hair with verticle mycelium externally and, underneath, a pus cell layer. The scutula may remain isolated, or form dirty crusts on coalescence. If this impetiginous crust is removed, the yellow color appears. The odor of old favus lesions is that of a mouse nest. The causative fungus is commonly *Achorion schoenleini* (*Grubyella*). However, Weidman (1937) distinguishes five species *Achorion schoenleini*, *galtinae*, *quickeanum*, *gypsum*, and *violaceum*. The evolution of the condition is slow. Some European dermatologists believe that the disease is contracted only during infancy

but that once it is acquired it never disappears entirely spontaneously. However, Brumpt reports that there are exceptions to this latter view. Sutton states that no age is exempt from infection. It is moderately infectious and spreads by direct contact.

The affected hairs are lusterless and greyish, and while more fragile than a normal hair can be epilated entire. Scarring may result. The favic hair is filled with air bubbles. The septate hyphal chains vary greatly in diameter (2 to 5μ). Cultures on Sabouraud's medium are like yellow beeswax and resemble cerebral convolutions. The growth is much slower than that of *Trichophyton*, and on microscopic examination there are fewer fuseaux. On the glabrous skin we may have scutula, but more commonly scaly patches. The involvement of the nails is rare and always follows lesions elsewhere (scratching). The toe nails are very rarely attacked. In the absence of a prior human case one must suspect infection from an animal source, particularly from mice, and caused by *Achorion muris*. This is a serious favic disease in mice, attacking the head and leading to blindness. In the human infection, the lesions are common on the body (like herpes circinatus) and also on the head. It is reported as common in Germany, less so in England and France. The classical favus is common in China and central Asia, but rare in Japan, England and America. In the United States, cases are more common in immigrants from Eastern Europe and it is also common in Mexico.

Eczema Marginatum and Ringworm of the Hands and Feet.—The above epidermophytoses are characterized by invasion of the horny layers of the epidermis alone. The ringworms of the hands and feet are generally caused by *Epidermophyton interdigitale*, and Hebra's eczema marginatum by *E. floccosum* (*E. cruris?*).

Epidermophyton and Endodermophyton Infections

We may separate the ringworms of the genera *Epidermophyton* and *Endodermophyton* from those just considered by the fact that they do not attack the hairs. Even in tinea imbricata, when the *Endodermophyton* spreads to the scalp, it always respects the hairs. In *Epidermophyton* infections the fungus is found, characteristically, in the stratum corneum of the epidermis, while with *Endodermophyton* the typical location is between the stratum corneum and the stratum lucidum of the Malpighian layer of the epidermis. These fungi never invade the corium.

The *Epidermophyton* dermatomycoses are wide spread in both temperate and tropical climates, while the *Endodermophyton* ones are strikingly restricted to the tropics. Manson's description of the fungus of tinea imbricata (Tokelau ringworm), from his studies of the morphology of the organism as seen in the scales, and his accurate report of the clinical course of the infection following human inoculation, is a classic.

The two genera are best differentiated culturally. In cultures of *Epidermophyton floccosum* there is a profusion of club shaped clostereospores (fuseaux), often in groups of 5 to 7, and divided by about 4 septa. With Endodermophyton there are no fuseaux.

Tinea Cruris

Epidermophyton Infection.—Under the name "*dhobie itch*," this fungus affection is probably better known to Europeans than any other tropical

skin disease. The name "dhobie" or "washerman's itch" has been given on account of associating it with the infection of the underclothing while being washed with the garments of those who have the affection. This view probably has some foundation, but it has been difficult to verify it. Hebra described the condition as eczema marginatum in 1860 and since that time very little has been added to his clinical description. It is also known under a variety of names, some of which are the following: dermatitis bullosa plantaris; dermatitis rimosa; Hong Kong foot; eczematoid dermatitis; dermatomycosis, tinea circinata, etc.

Epidemiology.—The organisms of dhobie itch seem to be wide spread if not ubiquitous. They are exceedingly common on the feet This mycosis spreads among the inmates of schools, barracks and gymnasiums and may be passed along by bathtubs and bathing tanks. The fungi live for long periods in shoes, slippers and socks and may be acquired from towels or perhaps by shaking hands. Some individuals seem to be more susceptible than others, and it has been suggested that differences in this respect may be due in part to the different activity of the sweat glands.

FIG. 257.—Tinea cruris. (From Mayer.)

Symptomatology.—The favorite site is the crotch, although the axillary region is also frequently involved. The process starts as minute papules, but these rapidly develop and give rise to angry red, swollen patches with sharply delimited margins. These red, festooned patches are usually limited to the perineum, scrotum and inner surfaces of the thighs. The itching is often distressing and many secondary infections or eczematous lesions result from the fierce scratching of the parts. If the patient goes to a cooler place, the process may subside only to return when he comes back to the hot, moist climate where the infection was originally contracted.

In some cases the fungus invades the region between the toes and gives rise to very intolerant itching and, from secondary bacterial infections, to a condition known as "mango toe." Other favored sites for the growth of these fungi are along the outer and inner borders of the foot, in the plantar concavity opposite the instep, and in the crease between the buttocks. The lesions on feet are well known under the designation of "athlete's foot." They frequently spread into the interdigital spaces of both hands and feet, thence spreading to the palms and soles. Eczema, pompholyx, cheiropompholyx and a number of other names have been given to these hand and foot manifestations.

Dodge gives *E. interdigitale* as the principal cause of epidermophytosis of hands and feet and *E. floccosum* as that for eczema marginatum. The growth of the interdigital

fungus is more rapid than that of the one affecting the inguinal and perineal regions. Numerous cases of *Eczema marginatum* and extensive lichinified eruptions of the skin have been reported in the Far East and in the United States as due to the species *Trichophyton (purpureum) rubrum* by Lewis, Montgomery and Hopper (1938) and by Swartz and Conant (1940). In the body ringworms, scrapings should be obtained from the borders of the lesions, and in the interdigital ones, preferably, from the small, grayish-blue, sago grain-like vesicles, if present. The material should be cultured and examined microscopically in caustic potash mounts.

Diagnosis.—The diagnosis of mycotic affections of this type should always be confirmed by the microscope. Fortunately the microscopic diagnosis is quite simple and usually successful. All that is necessary is to take a small portion of epidermis from the periphery of the lesion or the roof of the vesicle and immerse it for a sufficiently extended period (½ to 24 hours) in a 15 per cent solution of NaOH. This is done on a slide, the preparation being covered with a cover glass and sealed with vaseline if the longer period of observation is required. The larger the portion of epidermis taken for examination, the longer the time required for a satisfactory clearing. Figure 256 shows the appearance of the moulds in such a preparation.

Prognosis.—Except through superinfection, these mycotic affections are never dangerous to life. The fungi imprisoned in scales have been said to survive for over a year, so that a patient might be reinfected from his own shoes, slippers, etc. As the organisms multiply in the epidermis, they may live and carry over infection to more favorable sites without ever being thrown off from the skin. Hence the advantage of using medicaments in the chronic forms of mycosis which will keep the lesions desquamating mildly.

Treatment.—Tincture of iodine and salicylic acid have been found of great value in the treatment of this group of mycoses. When the lesions are fulminant and bacterially infected, the inflammation may be treated with mild antiseptics and of these potassium permanganate solutions have a well deserved reputation.

Stitt believes that the other types are often favorably treated with tincture of iodine, either full strength or diluted to suit the case. For chronic mycosis of the feet, a thorough painting of the sides, plantar surface and between the toes, paying particular attention to the toe nails, once every two weeks will keep the condition subdued when nothing else will serve. In such cases, the caution should be observed to stop the action of the iodine after from 10 to 15 minutes by immersing the foot in water and scrubbing vigorously with soap. This treatment causes superficial desquamation during the following week. An ointment of cold cream applied at night will facilitate this treatment. All vesicles should be punctured before applying the tincture of iodine. Soft corns are frequently successfully treated with tincture of iodine.

A common method of applying salicylic acid in this class of mycoses is in the form of Whitfield's ointment. It is composed of salicylic acid 6 per cent, benzoic acid 12 per cent in vaseline. The ointment may be used full strength or diluted.

Other medicaments which have been recommended are thymol, resorcin, ammoniated mercury, eucalyptol, phenol, and thymol iodide (aristol).

Manson-Bahr and others have recommended in severe cases chrysophanic acid ointment 20 grains to the ounce of vaseline, repeated twice a day until a slight erythema shows at the edge of the diseased edge. Chrysophanic acid, however, will stain the clothing and its use must be discontinued, as soon as the erythema appears as it is very irritating and should not be used on the face. It may be combined with chloroform and liquid gutta percha and painted on the skin with a brush on alternate nights:

Acid. chrysophan..............................	gr. xx	(1.3 grm.)
Chlorof..............................	ʒi	(3.5 cc.)
Liq. gutta-perchae..............................	℥i	(28.42 cc.)

A synthetic preparation of chrysarobin which is known as cignolin is said to be free from toxic action on the kidneys and can be applied to the scalp without danger of conjunctivitis. It is frequently prescribed with tar, as in the following prescription:

Ol. cadin. (deod.)	♏xl	(2.368 cc.)
Cignolin	gr. iv	(0.259 grm.)
Benzol. rect.	℥i	(28.42 cc.)

Another preparation especially recommended for treatment of "athlete's foot" is merthiolate cream, Eli Lilly & Co.

The infected patient should take every precaution against the spread of the fungus and should wear fresh paper slippers which can be burned.

X-ray therapy has been reported as of great value, particularly in cases in which the infection involves the fingers or toe nails. It has also been especially employed in *Tinea infection of the scalp* in children where it is often essential for successful treatment to remove the infected hair. Wise and Sulzberger (1937) state X-ray epilation is safe and sure if done by an expert.

Applications of barium sulphide with equal parts of zinc oxide and starch moistened and applied for a few minutes (only) has sometimes been employed, while other dermatologists have performed epilation with forceps. Formerly the production of a temporary allopecia in the treatment of ringworm of the scalp by the administration of acetate of thallium was noted. However, as Sabouraud demonstrated this substance is most poisonous in overdoses, the toxic dose is near to the dose efficacious for the production of epilation and a number of deaths followed its use. It is believed the drug has an effect on the endocrine system as well as on the sympathetic nervous system. Iodide therapy is advisable as an antidote in poisoning. It is now recognized that no one over 11 years of age can be given the drug with safety. Ingram recommends a single dose of not over 8.5 mg. per kilogram of weight. The dose should not be repeated for at least two months. The hair loosens and falls out from 12 to 24 days after the drug has been taken and the new hair begins to grow by the 25th day. This method of treatment is apparently still employed extensively in parts of Russia and in Spain and Mexico, to a less extent in England and the United States. Percival (1932) states that the average duration of the course of treatment with X-rays is about 135 days, while that of acetate of thallium is about 113 days. Brumpt believes that in certain rural districts where X-ray treatment cannot be obtained the acetate of thallium is the most practicable method of treatment.

Treatment with vaccines made from the fungi have not definitely been proved of value.

Tinea Imbricata (Malabar Itch, Tokelau)

Endodermophyton Infection.—This form of tropical ringworm is found chiefly in the islands of the South Pacific and in the Malay Archipelago. It is also found in southern China, southern India, and Ceylon. It has been reported from Colombia, Brazil and from Guatemala by Figueroa and Conant, (1940).

On account of the disease having been carried from the Tokelau Group to Samoa it is often designated *tokelau*. Manson was the first to recognize the affection as due to a fungus which he demonstrated microscopically in the scales. The specific cause of tokelau is *Endodermophyton concentricum* (*Trichophyton concentricum*).

He was also able to transmit the disease by inoculation experiments and found that after about ten days a raised, brownish spot appeared at the site of inoculation. This spot increased in size until when about one-fourth inch in diameter its central portion became detached, thus giving

rise to several thin, rosette-like scales, free at the center but still attached peripherally. The fungus advances peripherally, leaving a smooth surface within. Also there is a similar process developing in the original central spot again, to form a circle of scales within the older and more peripheral circle. The process is repeated until several rings of scales are formed each originating from the central focus as concentric ripples form on water from the fall of a pebble.

These scale circles are from one-eighth to one-half inch apart and give a festooned appearance to the affected skin. It was formerly supposed that the causative fungus was *Aspergillus concentricus* but Castellani has demonstrated that fungi of this genus, when present, are merely accidental. He has isolated in cultures what he considers the causative fungus, *Endodermophyton concentricum.* Scales were treated for 10 minutes with absolute alcohol and then a single scale was placed in each of a series of tubes of maltose bouillon.

The fungus grows between the rete malpighii and the external epidermal layers forming a network of mycelial threads, about 3 microns broad.

Another fungus that has been cultured from tinea imbricata scales is *Endodermophyton* (Trichophyton) *indicum.* Inoculation of this organism in pure culture has produced the disease.

Da Fonseca has isolated, in Brazil, from a dermatosis called *chimbere,* a species which he named *Trichophyton roquettei.* It is perhaps identical with *T. concentricum.*

The characteristics of the genus *Endodermophyton* are: The growth of a mycelial network between the rete malpighii and the superficial epidermal layers; in cultures only mycelial filaments are found; there are no conidia-bearing hyphae. Conant (1940) thinks the genus *Endodermophyton* should be dropped and the organism classified in the genus Trichophyton as in earlier years.

When this skin disease is introduced into a country with high relative humidity and fairly uniform temperature, between 80° and 90°F. it spreads with great rapidity. A dry climate or one showing considerable variations in temperature is not favorable for its spread.

Symptomatology.—The clinical characteristic of this form of ringworm is the presence of rosette-like lesions of several concentric circles of shingle-like, papery scales which are fixed peripherally and free toward the center, thus, from its imbrications, suggesting the name given it by Manson.

If one passes the finger over the affected surface from without inward there is no sensation of roughness but if passed from the center outward the free borders of scales cause a sensation of roughness. As these circles extend peripherally they meet the peripheral rings of other circles so that various curves appear which give the general appearance of watered silk. The flaky scales are of tissue paper thinness and are of a dirty, brownish-gray color. The general health of the patient is not affected but the itching is very severe. There is an entire absence of inflammation about this ringworm thus differentiating it from the more common tropical ringworms. Again the axillae and crotch are much more rarely affected than in other ringworms as is also true of the face, palms of hands and soles of feet. The scalp is never affected. Some claim that the fungus never

invades the nails but Manson states that this frequently occurs. The presence of the fungus in a scale treated with 10 per cent solution of sodium hydrate differentiates the scales from those of ichthyosis. Tinea intersecta is somewhat similar to tinea imbricata when first appearing, showing dark brown patches but it never shows the concentric rings. The ordinary ringworms present inflammatory characteristics.

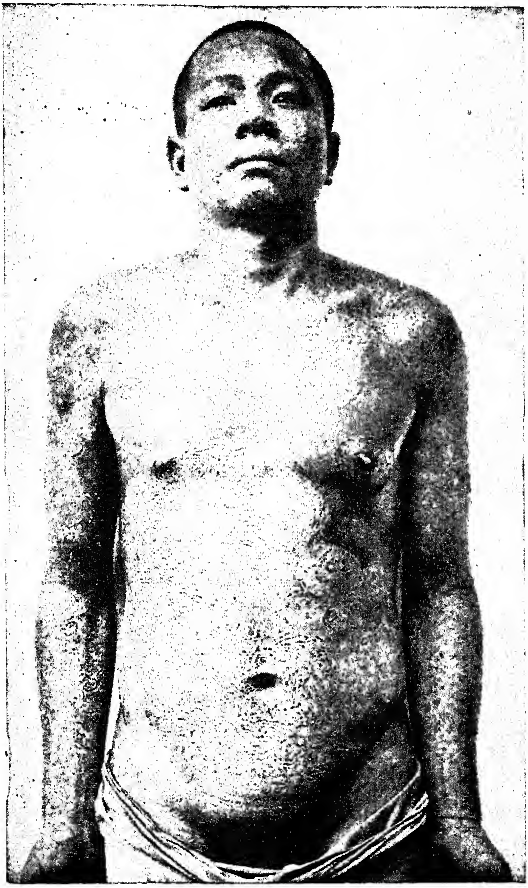


FIG. 258.—Tinea imbricata. (After Henggeler.)

Treatment.—A thorough preliminary scrubbing with soap and water in order better to expose the fungus to curative applications is important. Manson recommended iodine liniment. This contains 12½ per cent of iodine as against 7 per cent for the tincture. The liniment has also 3½ per cent of glycerine which is not an ingredient of the tincture. Both tincture and liniment have 5 per cent of potassium iodide. The application of the tincture does not seem to be as satisfactory as the liniment, the stronger preparation being more effective.

Chrysarobin is very effective but very irritant and has to be used with care. An application of a 5 per cent solution of chrysarobin in chloroform

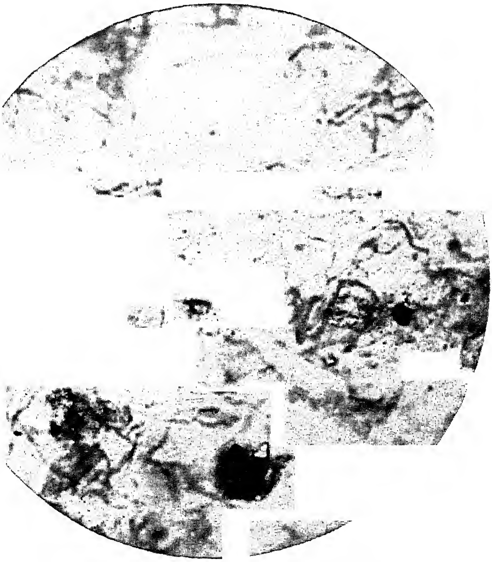


FIG. 259.—Tinea imbricata in the skin. (Philippine case.)

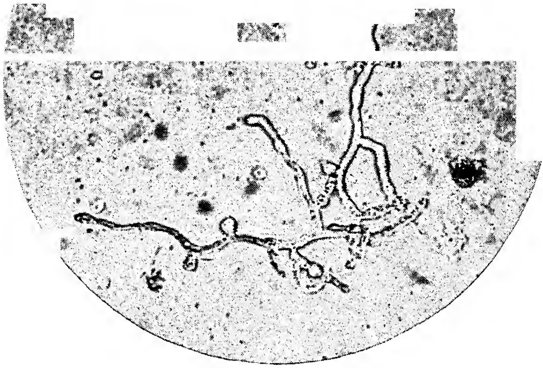


FIG. 260.—Trichophyton concentricum culture. (Manila.)

to the affected area, then painting it over with a 50 per cent aqueous solution of ichthyol, often gives good results. Some prefer a 2 per cent to

5 per cent ointment of chrysarobin. Chrysarobin produces a conjunctivitis if used near the eyes. Again if absorbed it may act as a renal irritant. The more modern preparation known as Cignolin (Bayer) may also be employed.

Castellani strongly recommends the use of resorcin in tincture of benzoin (60 to 120 grains of resorcin in 1 ounce of tincture of benzoin). Either remedy alone has very little effect, the combination being necessary. The application is made once or twice daily. In addition to this treatment the patient should be scrubbed with sandsoap and hot water twice a week. As regards prophylaxis the clothing should be boiled or burned. The natives attach value in preventing the disease to anointing the body with cocoanut oil.

The Aspergilloses

Various affections of the skin (including the mycetomas) and of the ear and lungs have been reported as aspergilloses. The Aspergillaceae family, to which belong the very common saprophytic fungi of the genera *Aspergillus* and *Penicillium*, frequently cause contamination of bacteriological plates and other cultures.

These colonies, together with those of the yeasts, mucors and spore bearing bacteria, should be familiar to every laboratory worker. Just as the various species of the Aspergillaceae contaminate a plate, so do they at times find a suitable soil in skin, ear or lung lesions, and many of the mycological authorities question the importance of these fungi as primary excitants of disease. In this family we shall consider the genera *Aspergillus*, *Penicillium*, *Scopulariopsis* and *Allescheria*. In the study of cultures and microscopical preparations of fungi, it is assumed that the worker is familiar with the more or less round vesicle of *Aspergillus*, with its phialides (sterigmata) and the chains of conidia branching off from them. In *Penicillium* these conidial chains extend from a conidiophore (sporophore), which does not spring from a vesicle. It somewhat resembles the skeleton of a hand, including the carpal and metacarpal bones, as well as the phalanges (represented by the chain of spores). Material for microscopical preparations is abundantly at hand in the patches of moulds on decaying fruits or vegetables, as well as in contaminated plates. The very common blue-green mould is a *Penicillium-P. crustaceum*. Another species, *P. brevicaule*, when grown in material containing arsenic, produces a strong odor of garlic, and is the basis of a very delicate test for arsenic—1 in 1,000,000.* The very black moulds will in many instances show the fruiting bodies of *Aspergillus niger*. *A. oryzae* saccharifies the rice starch (diastase) and, in symbiosis with a yeast, produces the 15 per cent alcoholic drink "sake" of the Orient.

Other fungi of this family are of great commercial importance. In material from sputum, pus or skin scrapings, we find a morphology which does not resemble the fruiting bodies obtained when one cultures this material in media containing fermentable carbohydrate, hence the study of pathological material should always include cultures. The evidence of the production of primary disease by any species of this group is not entirely convincing. *Aspergillus fumigatus* has been reported as responsible for an epizootic in pigeons; and pigeon-feeders have developed aspergillosis. This infection has also been found in parrots and it was formerly thought it might be concerned in the lesions of psittacosis now known to be due to a filtrable organism. In addition, it has been isolated from cases of human broncho-pneumonia. Castellani reported species of both *Aspergillus* and *Pencillium* and also *Monilia* as a cause of bronchomycosis.

* The species of Penicillium, which Fleming (1929) demonstrated, caused lysis of staphylococcus colonies, has been identified by Thom as *Penicillium notatum* Westling. It is probably a soil mould. The active principle of the mould was next isolated and was found to be freely soluble in water and was named Penicillin. The substance has proved to be of exceptional value in the treatment of a number of cases of fulminating pyogenic infection. Reports have been made of its great value in the treatment of infections produced by *Staphylococcus Aureus*, *Pneumococcus*, *Hemolytic Streptococcus* and the *Gonococcus*. In general it is ineffective against gram-negative organisms. Exceptions to this rule are the Gonococcus and the Meningococcus. The results obtained in the treatment of gonorrhea with penicillin are described as spectacular. It is prepared for intravenous use, for intramuscular injections, and for local use in the treatment of wounds. It is supplied for clinical use as the sodium salt. (See also pp. 355, 376, 1109a, & 1175.)

The pulmonary infection is said to resemble phthisis, but the patient generally does not seem to show an illness entirely comparable to tuberculosis. Haemorrhages are frequent, and at other times the sputum tends to be blood-streaked. Cases of aspergillosis have been reported, with nasal and corneal lesions; in the latter case the injury has been from scratches by plant material. *A. unguis* has been reported as the cause of a mycosis of the great toe.

Mood (1938), in a study of 32 cases of otomycosis observed in South Carolina, isolated species of *Aspergilli* from 31 and a species of *Penicillium* from one. Gill has also found a species of *Mucoracea* in infections of the ear. Mood believed that treatment

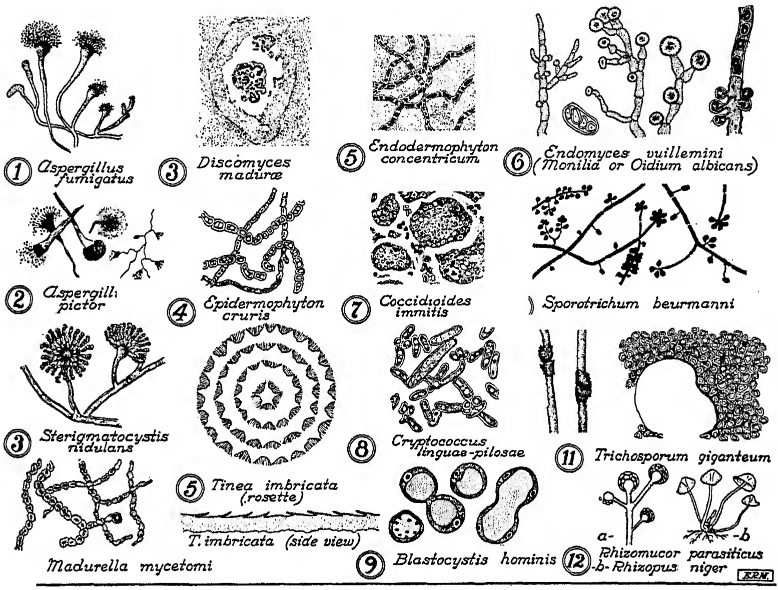


FIG. 261.—Important tropical fungi.

with a vaccine made from the infecting fungus lessened the discomfort and restored the ears to normal quicker than the usual treatment and that recurrences were less frequent.

Mycetomas.—While tumors produced by fungi have been preponderantly connected with species of *Actinomyces*, yet cases have been reported by Brumpt and others where the findings were those of *Aspergillus* or *Pencillium*, and Negroni (1939) has reported the isolation of a species of *Aspergillus* in a case of mycetoma in Argentina. While the evidence for pathogenic action of *Pencillium* is usually slight, this cannot equally be said for *Scopulariopsis*, which morphologically greatly resembles *Pencillium*. Species of this fungus have been reported from cases of onychomycosis. Markley, Philpot and Weidman (1933) have reported the isolation of *S. brevicaulis* from a case of ulcerating granuloma and successfully inoculated animals with the organism. Apparently this is the first case described in the United States. *S. koningi* was reported from a gummatous lesion of the hand and, in several instances, from trench foot.

The Maduromycoses

MYCETOMA (MADURA FOOT)

Definition.—Mycetoma is the result of a fungus infection especially of the foot and more rarely of other parts of the body. It is characterized by swelling and hypertrophy of the tissues resulting in a deformity of the part. The affection is chronic and recovery does not occur spontaneously. Surgical removal or amputation is the only successful method of treatment.

Classification.—Van Dyke Carter established the fungus nature of Madura foot, a common affection in the Madras Presidency of India. He applied the designation "mycetoma" to the disease, and Chalmers and Archibald divided mycetomas into two groups: (1) Maduromycoses, with granules containing large, segmented mycelium, with well defined walls, and often chlamydospores; and (2) Actinomycoses, with granules composed of very fine, non-segmented filaments, with ill-defined walls and no chlamydospores. They also recognized a paramycetoma, in which the fungus did not produce granular aggregations. The maduromycoses have been separated on the basis of the color of the granules—black, white, yellow and red. These grains may be embedded in the tissues or present in the discharge from the sinuses. Usually only one kind of fungus is found in a single case. Brumpt, in 1906, described 8 species, but in 1936 he listed 48 species as capable of producing the clinical aspect of mycetoma and suggests that there may be still others. He also divides the mycetomas into two groups, the maduromycoses and the actinomycoses. In the maduromycoses he lists 30 species in 14 genera. The mycelium of *Madurella* is septate and branches from time to time. It is much larger than that of *Actinomyces* (usually less than 1μ in diameter while the hyphae of *Madurella* are always above 1μ and may reach a diameter of 8–10μ. Two cases of white mycetomas have been reported as caused by species of *Indiella*—*I. mansoni* (India).

History and Geographical Distribution

History.—The disease was first described by Kaempfer about 200 years ago, but at that time was often confused with elephantiasis. The first exact clinical description of the disease, with its pathology, in which was noted the fungus nature of the granules given off in the discharges from the sinuses, was that of Van Dyke Carter, whose studies were carried on between 1861 and 1874.

Geographical Distribution.—The name Madura foot takes its origin from the great prevalence of the affection about Madura, in the Madras Presidency of India. It is also endemic in other and widely scattered districts in India, as Delhi, Kashmir, and Rajputana. It also occurs in Ceylon and cases have been observed in Cochin China, (Piede de Cochin). Four cases have been reported in the Dutch East Indies by Boers, Kouwenaar, Wolff (1938). The disease is rather widespread in Africa, having been reported from Algiers, Tripoli, Tunis, Egypt, the Sudan, Aden,

Somaliland, Senegambia and Madagascar. Cases have also been reported from Italy and Greece in Europe and from the West Indies and some of the South American countries, notably Argentina and in Cuba. Sutton, in 1913, reported 2 cases from Kansas, one in a Mexican and one in a native of Texas while Hanan and Zurett (1938) a case in New York in a Hindu. Boyd and Crutchfield have collected 30 cases from the literature.

Etiology and Epidemiology

Etiology.—The disease is caused by the penetration of certain species of fungi into the tissues of the foot, as by puncture of a thorn or through

FIG. 262.—Mycetoma (Madura foot).

other abrasions. Rarely the hand or some other part of the body may be affected. The fungus develops in granulomatous areas from which sinuses lead to the surface of the foot, in the discharges from which are found small granules resembling those found in the discharges from actinomycosis lesions.

A very common infection is that due to *Actinomyces madurae* (*Discomyces madurae*) which is a fungus with fish-roe-like granules of the pale or white variety of mycetoma. These, like the fungus of actinomycosis, *Actinomyces bovis* (*Discomyces bovis*), show a felted mycelium in the center and peripheral club-like structures. The granules are yellowish-white and vary in size from a pin's head to a small pea. The mycelial threads are very narrow, 1 to 1.5 microns. The ends break up into ovoid conidia 1.5 to 1.75 microns in size. The organism grows aerobically and the

cultures show slender mycelial threads which are Gram-positive. It is not pathogenic for animals. This is the organism of Carter's white mycetoma.

Other species of the pale, white or ochroid group of mycetoma fungi are *Indiella mansoni* (Brumpt's white mycetoma), *Actinomyces asteroides* (*Nocardia asteroides*) (Musgrave and Clegg's white mycetoma), *Sterigmatocystis nidulans* (Nicolle's white mycetoma) and several others.

The cases caused by the black varieties are characterized by the presence in the discharges from the sinuses of black gun-powder-like grains. These hard, brittle, irregular grains are caused by various species of fungi of which the most common is Carter's black mycetoma (*Madurella mycetomi*). This species was cultured by Wright and first shows a grayish growth, later becoming black. Other black varieties of mycetoma are

FIG. 263.—Section from a Madura foot. (After Fülleborn.)

due to very different fungi. Bouffard's black variety is caused by *Aspergillus bouffardi*. DeBeurmann's black mycetoma has been reported to be due to *Sporotrichum beurmanni* (*Rhinocladium beurmanni*).

Besides the white and black varieties a red variety of mycetoma also occurs. The fungus grains are quite small and reddish in color. It is not an uncommon infection in certain parts of Africa, as Senegal. The cause is *Actinomyces pelletieri*.

Boyd and Crutchfield have noted an ascomycete in an American case, with white granules, to which has been given the name *Alleschiria boydii*. Negroni and Tey (1939) have reported the first case of mycetoma infection, (maduramycosis), from Argentina, from which they cultivated *Aspergillus chevalieri* (Mangin, 1909). Costa (1941) has reported the 4th case in Brazil.

Trebedi and Mukherjee (1939) have reported 3 additional cases to the 32 which have been collected at the Medical College in Calcutta. In

two of these the fungus isolated was the species *Actinomyces madurae* with the ochroid type of granules. In the third, the species was apparently not identified.

In recent years the organisms giving rise to both mycetoma and to actinomycosis have generally been classified in the one genus *Actinomyces*, in which some 76 species have been described. The characteristics of the genus and of a few species which have been isolated are referred to in the next section, p. 1185.

However, a number of fungi other than actinomyces have been described as capable of causing the disease.

Niño (1941) has reported a case in Argentina with white grains in which the organism isolated was classified as *Monosporium apiospermum*. Shaw and MacGregor (1935) have also reported a case due to this organism in Canada, while Almeida and Barbosa report the isolation from a case of mycetoma in Pernambuco *Cephalosporium recifei, Leao and Lobo*. They note that this is the first case of mycetoma attributed to a species of this genus.

Epidemiology.—We know very little about the occurrence of these mycetoma fungi, other than in man. It is thought that such fungi lead a saprophytic existence on thorns or blades of grass or spine-like grains of various cereals. Thus Nicolle's case in Tunis started from a puncture wound by a grain of barley.

As the vast majority of such cases are noted in the feet, and as such cases are chiefly in those who work barefooted, it seems reasonable to consider that the fungi are introduced by some puncturing object and the external wound having healed, development goes on in the deeper structures.

Pathology

In more than 75 per cent of cases of mycetoma the foot is the only part infected. Rarely there is involvement of hands, knees and buttocks. The affected part shows nodules on the external surface which connect with the granulomatous lesions of the interior of the foot by sinuses. In advanced cases there may be a network of sinuses and cyst-like dilatations, which are filled with a viscid fluid packed with the small fish-roe granules in the white variety, or with the gunpowder grains in the black mycetoma. The bony structures of the foot may undergo disintegration as well as the muscular and areolar tissue so that on cutting into such a foot there is nothing normal remaining—often a cheesy mass.

In the early granulomatous areas there are found the actinomyces-like granules surrounded by an area of mononuclear and polymorphonuclear infiltration. Giant cells are occasionally found. There is an inflammatory oedema. Externally there are connective tissue cells and a fibrous wall. The blood-vessels show endothelial proliferation and thrombosis. Visceral metastases do not occur.

Symptomatology

The disease usually begins in the sole of the foot with the formation of firm swellings about ½ inch in diameter. The cases are rarely seen at this stage, the natives waiting before seeking medical advice until the nodule has softened and begun to discharge the viscid fluid with the various-colored granules floating in it. As stated before, the soft, yellowish-white, fish-roe-like granules are most commonly observed, the more friable, hard, gunpowder-like grains less so. The nodules continue to form and to break down until the foot has become greatly enlarged, the

under surface bulging out in a convex mass with the toes and heels appearing as if raised. The dorsal surface is also puffed up and studded with broken down nodules, and the sides well rounded. There is no increase in the length of the foot. This swollen distorted foot is borne on a thin peg-like leg which makes the size of the foot more striking. Very rarely cases have been reported where the hand or thigh has been involved. If one probes the discharging sinuses bone may or may not be felt according to the advancement of the degenerative changes. There is rarely pain or bleeding following the probing.

It is more from the burden of carrying around this fungoid mass of a foot, 3 or 4 times the normal size, than from pain, that the patient complains. Uncomplicated cases do not show fever and the occasional enlargement of lymphatic glands is probably connected with bacterial infections. There are never visceral metastases in mycetoma as is true of the nearly related actinomycosis.

The process shows no tendency to heal naturally or under treatment but fortunately does not extend, the process being confined to a foot or a hand. The joints are rarely if ever invaded. Unless the sinus-riddled member is amputated the drain on the patient gradually exhausts him and death ensues in ten or fifteen years.

Diagnosis

The distorted appearance of the foot or hand, riddled with sinuses discharging a viscid fluid containing the variously colored granules, which upon microscopical examination are found to be sclerotia of fungi, is absolutely diagnostic. As regards recognition of the causative fungus one should culture the discharge or grains on maltose agar, potato or rather dry blood serum. The recognition of these species of fungi is a very difficult matter, even for an expert.

Prognosis

This is absolutely unfavorable as regards the relief of the condition but as regards life it is not unfavorable provided the drain on the system is gotten rid of by amputation of the part.

Prophylaxis and Treatment

Prophylaxis.—The wearing of shoes in the fields or forests would seem to be the best means of protection against small wounds from thorns, splinters and the like.

Then, too, any such wound which might occur should be treated with tincture of iodine.

Treatment.—Curetting the lesions may be tried. As a rule, the process goes on, but is limited to the member attacked, so that amputation of the diseased part brings about a cure. Iodide of potash is apparently often ineffective, as is the use of thymol. X-ray treatment seems to be of value in relieving the pain and in lessening the discharge from the sinuses, but

is of questionable curative effect. It might be of greater value if tried early in the disease.

ACTINOMYCOSIS

Actinomycosis, or lumpy jaw, is a fungus infection of man or cattle caused by *Actinomyces bovis* (the Ray fungus). It is characterized by the formation of granulomatous connective tissue and by multiple abscesses giving rise to an exudate containing characteristic yellowish granules.

FIG. 264.—Streptothrix madurae (Vincent), pink variety of mycetoma. (Isolated by author. Musgrave and Clegg.)

History.—Bollinger (1877) demonstrated that the disease of cattle known as lumpy jaw and regarded as a form of sarcoma is due to a parasite which was named by Harz *Actinomyces bovis* because of the radiating structure of the organism. J. Israel (1878) found the fungus in man, and the following year Ponfick pointed out the identity of the human and bovine infection, while Wolff and Israel first gave careful descriptions for the identification of the organisms encountered in the lesions.

Any tissue or organ may be attacked. Lesions of the head and neck are most common and occur in some 60 per cent of the reported cases. The abdomen is infected in some 20–30 per cent, often in relation to the appendix or caecum, and the thoracic cavity in from 10–15 per cent.

Kessel and Goolden (1938) have recently made a comparison of *Actinomyces* strains recovered from human lesions in the United States. They point out that some 76 species have been described as isolated from human lesions. Some of these are described as being aerobic and some as anaerobic, but in many instances the descriptions are not given in sufficient detail to be of value in actual classification. Some consider the anaerobic forms as the true pathogens and the aerobic ones as saprophytes.

Classification.—Bergey, in his "Determinative Bacteriology" (1939) classifies the genus *Actinomyces* with *Mycobacterium* (tubercle bacillus) and *Corynebacterium* (diphtheria bacillus), genera definitely belonging to the *Schizomycetes* or true bacteria. He, however, makes the separation into 2 families (1) *Mycobacteriaceae*, including the diphtheria, tubercle and leprosy bacillus, and (2) the Actinomycetaceae. In the latter family he classifies the genus *Actinomyces*.

The family of Actinomycetaceae is so widely distributed in nature (in the soil, on plants and in the faeces of man and animal), and so important in biological processes, that its careful study has been the province of biologists, rather than those interested in human or veterinary medicine, and there has been rather general agreement among them to assign this group of organisms to the domain of mycology.

Characteristics.—*Actinomyces* resembles bacteria in many respects, of which the following may be noted: (1) The diameter of the mycelial threads rarely exceeds 1μ (usually 0.5 to 0.8μ). (2) The sparsely and irregularly septate filaments of *Actinomyces* tend to break up into bacillary or coccoid forms. This fragmentation has been interpreted as arthrospore formation, and in some species chains of spores are noted. The sporogenous hyphae frequently show a coiling of several turns (rarely exceeding 12 spirals), which may be to the right or left. The spirals uncoil after the maturation of the spores. Variations in spirals are of importance in the separation of species. All species are non-motile and Gram-positive. Some species, when grown on fat-containing media, may show acid-fast staining.

It must be kept in mind that many of the attempts at culturing the acid-fast leprosy bacillus have resulted in streptothrix (*Actinomyces*) growth, and Deycke's nastin (a much vaunted cure for leprosy) was an ethereal extract of such a streptothrix growth obtained by culturing leprous nodules.

In common with other mould contaminants of bacterial plate cultures, we frequently find leathery, very adherent colonies of *Actinomyces*, which may be chalky or show various colors—yellow, red, black or green. When transferred, such colonies give off a musty, earthy odor. In medical mycology a separation on the basis of oxygen requirements has been used, one group requiring anaerobic conditions for growth and the other growing under aerobic environment. The pathogenic species attaching to actinomycosis in man, or "lumpy jaw" in cattle (the Israel type), belongs to the anaerobic group. The requirements are rather those of partial oxygen tension than complete anaerobiosis. J. H. Wright stressed the necessity for choosing as material for culture that which contained filamentous organisms (observed by pressing between two slides), and then inoculating glucose agar stabs.

Growth first appears one or two cm. below the surface. Bacterial contaminants are frequently responsible for failure. Growth is first noted as a small white speck, after three days, at 37°C. It would seem probable that the aerobic species are largely saprophytic. The *Actinomyces* genera of mycetoma seem, however, to be mostly aerobic. Bostroem has claimed that he has isolated an aerobic fungus from actinomycosis but his work, generally, has not been confirmed. Wright called the aerobic group *Nocardia* and the anaerobic one *Actinomyces*. Other recognized genera are *Streptothrix Oospora* and *Discomyces*.

Clubs and Granules.—In the pus from lesions there occur the sulphur granules in actinomycosis, and the black (gunpowder) ones in Madura foot. Mycetomas caused by other fungi may show granules of other colors. The granules of *A. bovis* rarely exceed 150μ in diameter and are of a yellowish white color. The granules of *A. madurae* are of an ochroid color and this species gives rise to white mycetoma. The fungus of the black grain variety of mycetoma is *Madurella mycetomi*. These granules (when small and crushed between slides) show a central filamentous mass with bulbous structures set peripherally (usually called "clubs"). Dodge considers these granules as bulbils (small sclerotia). Clubs are rarely seen in cultures. It is from the peripherally placed bulbous extremities that we get the name "ray fungus."

Clinical Manifestations.—There are four main types of actinomycosis in man—(1) Cutaneous, where an epidermal lesion invades the corium and subcutaneous tissues producing a nodule which breaks down and dis-

charges fish-roe granules. (2) Buccal. In cattle the invasion of the jaw has given this actinomycosis the name "lumpy jaw." The process extends to the adjacent soft parts. The tongue is involved in almost one-third of these cervico-facial types. (3) Usually secondarily to buccal infections we have a pulmonary type, usually fatal, while the purely buccal ones, which can drain freely, generally recover. (4) The intestinal type, usually in the region of the caecum and appendix (diagnosis commonly appendicitis). The actinmycotic lesions are generally free from pain. Extension is by continuity—rarely by blood vessels or lymphatic channels. When enlargement of tributary glands occurs it is indicative of

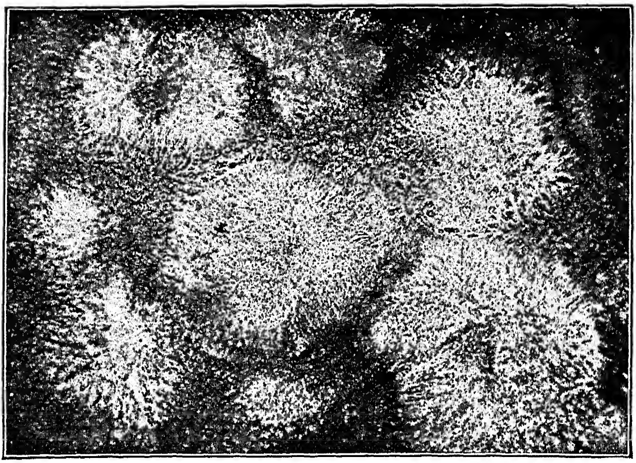


FIG. 265.—Actinomyces granule crushed beneath a cover glass, showing radial striations in the hyaline masses. Preparation not stained; low magnifying power. (McFarland after Wright and Brown.)

Actinobacillus infection. The diagnosis of actinomycoses depends chiefly upon laboratory examinations.

Epidemiology.—Heating to 60°C. is always fatal to these organisms, so there is no question of a resisting spore, as for anthrax. For many years the opinion was held that infection took place by inoculation of some wound produced by plant material (as a blade of grass or a cereal grain). In view of the fact that *A. bovis* is a rather delicate, anaerobic organism and grows only at body temperature, this idea is untenable. There is much to indicate that actinomycotic filaments may have as habitat the carious material in defective teeth or in tonsillar crypts. Naeslund (1925–1926) has isolated anaerobic strains from such material, which may be identical with *A. bovis*. He also considers tartar formation on the teeth as a possible source of infection.

Laboratory Diagnosis.—The fungus is to be found in the granules, and it is essential that culture or microscopical material be obtained from them. The purulent discharge may be poured in a thin film in a Petri dish and search made for these minute granules. They are best fished up with a capillary pipette and examined unstained, with diminished light, for the clubs of the ray fungus. In tissue sections Gram's stain is very satisfactory, although they show beautifully in ordinary haematoxylin-eosin stains. The method of culturing used by Wright is noted above. Very satisfactory is the use of the capillary portion of a rubber bulb pipette. The growth in this narrow casing can be satisfactorily observed under the microscope. Animal inoculation has not been

satisfactory, as Homer Wright was not able to satisfy himself of actual multiplication in laboratory animals.

More Important Species.—Dodge gives the characteristics and synonyms of 108 species of *Actinomyces* with a differentiating key.

A. Bovis.—This organism is generally considered the cause of lumpy jaw in cattle, and is present in the sulphur granules which are so characteristic of this infection. The fungus which is present in human actinomycosis seems to have the same morphological and cultural characteristics as that of cattle. As noted above, it requires partial O tension and body temperature for growth. The problem of etiology is complicated by the frequent association with actinomycosis of two bacterial organisms, *B. actinomycetem comitans* and the *Actinobacillus*. It is even maintained that many of the pathological changes present may be due to these companion organisms.

A. Madurae —This organism is the cause of white mycetoma (Carter or Vincent). The granules are white to yellow and the hyphae from 1 to 1.5μ in diameter. Authorities disagree as to cultural requirements. According to R. St. John-Brooks, it is a strict aerobe growing best at 37°C., but having a wide temperature range (20 to 40°C.). Dodge notes that it is a facultative anaerobe, but grows best anaerobically.

A. Asteroides.—This is a frequent cause of white grain mycetomas in various parts of the world. Some authorities give its cultural requirements as aero-anaerobic—others as aerobic, and still others as anaerobic. This fungus was first reported by Eppinger from a brain abscess and, apparently, the same organism has since been reported from mycetomas in the Philippines, Brazil, Argentine and Europe, as well as Asia and Africa. Brumpt gives it as Gram-positive and acid-resistant.

A. Gypsoides.—This organism was isolated by Henrici and Gardner from the sputum of a case of pulmonary mycosis. They noted its growth as more rapid than that of the tubercle bacillus and that it was acid-fast. For its recovery from sputum they recommended guinea-pig inoculation. Wright could not assure himself of multiplication of *Actinomyces* in guinea-pigs.

A. Keratolyticus.—This *Actinomyces* is given as the cause of cracked heels in India (keratolysis plantare sulcatum). It has also been found in interdigital erosions. It is said to be due to walking barefooted on damp soil covered with manure. The colonies on agar are pink or reddish.

A. Minutissimus.—This fungus has been reported as the cause of erythrasma (see p. 1165). Cultures are frequently negative. When successful the colonies on agar have been reported as wine red or brown-red.

A. Thuillieri.—This fungus was studied by Pasteur and Rosenbach (1883-1884). Bergey classifies it in a separate Genus *Erysipelothrix* Rosenbach, It was the first fungus with which proof of immunity was obtained. It seems to live saprophytically on fish. It causes a disease of pigs known as swine erysipelas, which may be communicated to butchers, veterinarians or others working with this pig infection. In Europe this disease of pigs is serious economically, but it is rather rare in the U. S. In Germany it is called *rotlauf*, and in France *rouget*. Besides the hog, the disease may be communicated by other animals, especially crabs. Most cases in the U. S. have come from handling crabs or fish taken in the Chesapeake Bay region. The human disease, *erysipeloid*, follows local infection of a wound of the skin. In a day or two a swollen, deep red area, with a bright red margin appears. Although the usual type of infection is cutaneous, rarely it may produce lymphangitis. Glandular enlargement may occur. Rarely, the infection may become generalized. The organism resembles the diphtheroids, but is now classed with the Actinomyceteae. Another name is *Erysipelothrix rhusiopathiae* and it was formerly called *B. erysipelatis suis*. It is easily cultured and on bile media shows filamentous forms, whereas in broth there are only bacillary forms. A *p*H of 7.6 favors growth. The infection seems to confer a lasting immunity. An antiserum has been produced which may be injected into the region of the lesion or intramuscularly.

Streptothricosis.—The lesions described in man under this term have been suppurative and resemble those of Actinomycosis with the formation

of abscesses and granulation tissue. The lung is the usual site of infection and there may be evidences of broncho-pneumonia, multiple abscesses, gangrene, bronchiectasis, or empyema due to the fungus. In some instances, metastases in the brain and subcutaneous tissues have been reported. Cases sometimes have resembled those of pulmonary tuberculosis or pyemia. All the cases in which the isolation of a *Streptothrix* has been demonstrated from the lung or sputum have died. The relationship of the genus *Streptothrix* (Cohn) (*Streptothrix* Corda) to *Actinomyces Cladothrix* and *Nocardia* is not entirely clear. The reported *Streptothrix* infections, unlike Actinomycosis, have been rarely about the head and neck. Bergey classifies these organisms in the genus *Actinomyces*. However, infections due to *Actinobacillus* are distinct and the organism classified in the *Bacteriaceae*.

Treatment.—Treatment of actinomycotic lesions is frequently unsatisfactory. The most satisfactory treatment has been obtained in cases when the diagnosis has been made early, when small, easily accessible lesions have sometimes been successfully excised. In other instances, curetage has apparently spread the infection.

Full doses of iodides and also thymol have been recommended for treatment, but in many instances no favorable results have been obtained with these drugs.

Lord (1937), and Cutler and Gross (1940) emphasize treatment with X-ray irradiations after radical removal of obviously diseased tissue.

Sulfonamide treatment has especially been recommended and 10 successful reports and only 1 failure have appeared in the literature since 1938 according to Benbow et al (1944). Hollensbeck, and Turnoff (1943) and Benbow recommend sulfadiazine as the drug of choice. Lyons, however, points out that long treatment is usually necessary and there is ever present danger of recurrence.

Important prophylactic measures are the care of apical abscesses, pyorrhea, and other dental and stomachic infections. Also, prompt and adequate disinfection should be given to punctured wounds, especially those in which foreign bodies have been implanted. The medical treatment of *Streptothrix* infections has also proved unsatisfactory.

Sporotrichosis

Sporotrichosis is a chronic infection, usually limited to the skin, subcutaneous tissues, and lymphatics, occasionally involving the muscles, bones, joints and lungs.

This gummatous or ulcerative mycosis, which usually follows the course of the lymphatics of forearm and arm, generally starts from a thorn prick of hand or phalanges. The causative fungi of the genus *Sporotrichum* are widely distributed as saphrophytes. The family of Sporotricheae is characterized by branched, septate mycelium. The spores, which are generally single and never in chains, project from the hyphae on short sterigmata, or are sessile.

From the standpoint of reported cases, France and the U. S. are the chief countries showing infection, but this may be connected with more frequent search for the fungus. Other cases are reported from South America and Africa. The isolation of the fungus from a sporotrichosis lesion was first reported by Schenck in 1898 (J. H. H. Bulletin), and later on was recognized as a clinical entity by Beurmann and Raymond (1903). Dodge assigns *S. schencki* as the name of the parasite, and considers *S. beurmanni* a variety. The hyphae are about 2μ in diameter. A difference between the two organisms has been noted in the frequent appearance of chlamydospores in the Beurmann fungus, and the rarity of such resistant spores in the Schenck fungus. In the pus or tissues of sporo-

trichosis lesions one never finds mycelium, but only cigar shaped, yeast-like bodies phagocytized in monocytes. For diagnosis one should always culture the pus or scrapings (preferably from an unopened lesion). The colony first appears about the second day, and a microscopic preparation shows the narrow mycelium with spores (3 to 5μ), usually in groups at the ends of the hyphae. Optimum temperature is from 30° to 38°C. Sporotrichosis is usually diagnosed as syphilis or tuberculosis, but development of the lesions is more rapid. There is also less effect on the general health, as well as a lack of glandular involvement. Cases of pulmonary sporotrichosis have been rarely reported, and also generalized infection. The lesions are usually confined to the deep parts of the skin or mucous membranes.

S. beurmanni is the commonest species reported from plants. It ferments saccharose, but not lactose. The spores are very numerous and often provided with short sterigmata.

Five other pathogenic varieties have been recently listed. Wolbach described a species isolated from an arthritis of the knee which he named

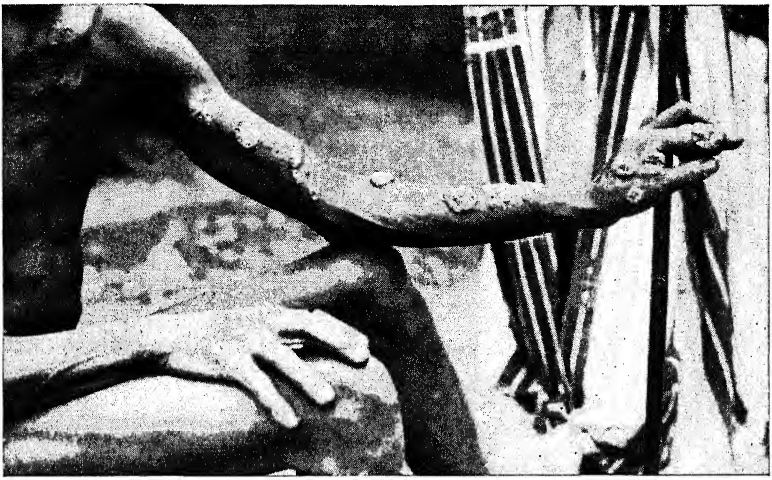


FIG. 266.—Sporotrichosis. African native.

S. councilmania. Spontaneous infections due to *S. beurmanni* have been observed in rats, dogs and horses. This fungus is unusual in its pathogenicity for both plants and animals. Benham and Kesten have transmitted sporotrichosis to carnations by inoculation of the plants with the culture of *S. schenki*, derived from an infection in man. The disease produced in carnations is a bud rot similar to that caused by the plant pathogen, *S. poae*. After living saprophytically or parasitically in plants, *S. schenki* retained its virulence for animals. Zinsser (1939) remarked that the successful experimental inoculation of barbary thorns accomplished by these investigators adds to the evidence that plants may be a natural source of this infection for man and that the disease may be contracted by puncture wounds with infected thorns or other pieces of plant tissue.

Laboratory Diagnosis.—Widal and Abrami have proposed an agglutination test, and others, skin tests, but the culturing technique is so simple

and satisfactory that it is given preference. An examination of the pus, microscopically, rarely reveals the cigar-shaped rods. A caustic potash mount is satisfactory if the large bacillary forms are present, but it is on the culture that one may have to depend for diagnosis. Sporotrichosis is often associated with tuberculous lesions. In the United States the majority of the cases, some 140, have occurred in the Mississippi River Basin.

Other cases have been described in South America. Campas and Almeida have studied 12 cases in Sao Paulo. Filho has named a species he isolated in Brazil, *Sporotrichum fonsecae*. Also, the writer (1930) isolated a species resembling *S. beurmanni* from ulcerative lesions of the arm in a case in Liberia.

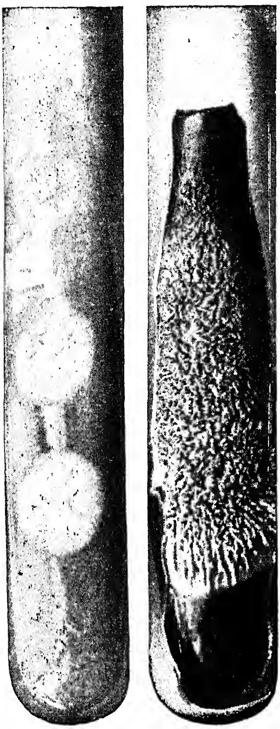


FIG. 267.—*Sporotrichum schencki*. Cultures on the glucose peptone agar of Sabouraud. (After Gougerot.)

Dangerfield and Gear (1941) have reported 74 cases in South Africa, 6 were in European miners, the remainder occurring in natives. From one mine there were 17 patients, most of whom worked in one shaft The rest all worked in one shaft of a second mine.

Sporotricheae in Tinea Albigena and Mycetoma.—A skin infection of hands and soles, later extending to arms and legs, seems quite prevalent in the East Indies. The fungus is *Aleurisma albiciscans*. A black grain mycetoma has been reported from the Soudan due to *Trichosporium khartoumensis*.

Treatment.—Sporotrichosis when uncomplicated is rarely fatal. However, if it is untreated it persists for months or for years. Treatment with iodide of potash is usually effective. The drug should be given in slowly increasing doses up to 4–6 gm. or more daily. Lord advises if it is not well tolerated by mouth it should be administered by rectum. If absorption of nodules or abscesses is slow they may be injected with a weak solution of the iodide. Ulcerated lesions may be painted with tincture of iodine. Incision of the nodules or curettage is not recommended as it may spread the infection. X-ray radiation has also proved to be of value in the treatment of the skin lesions.

Chromoblastomycosis.—Lane and Medlar (1915) reported upon a case which had been clinically diagnosed as verrucous tuberculosis. The lesions on the leg consisted of two small growths. Examination of the first showed a small tumor in the skin outside the ischiatic tuberosity. It was about 2.5 cm. by 2 cm. in diameter, purplish in color, raised about 3 mm. above the surface, the top of which was slightly grayish in places. There were a few gray scales on the lesion. There was no discharge at the time of the examination. The second lesion was one which had been previously operated upon. It showed, at the time it was examined by Lane, a purplish, slightly raised, rather soft area about 2 cm. in diameter,

freely movable and not tender. There was a small, crater-like opening in the center, from which there could be expressed a slightly gray, somewhat cheesy substance mixed with a little blood. In the microscopical examination, however, a fungus was discovered which was cultivated on the usual laboratory media and carefully studied by Medlar, and to which Professor Thaxter gave the name: *Phialophora verrucosa.*

Medlar found that the cellular reaction toward the fungus resembled very much a typical blastomycotic lesion. There was an inflammatory reaction varying from acute to chronic in type and a moderate increase of connective tissue. This process was most marked in the corium, but was also found to a slight extent intraepidermally. In the regions where the acute inflammatory reaction predominated, the exudate consisted chiefly of polymorphonuclear leucocytes and a deposit of fibrin, with an occasional endothelial leucocyte and eosinophile. As a general rule, in some portion of these miliary abscesses one or more microorganisms were present.

Pedroso and Gomez, in Brazil, in a case of verrucous dermatitis isolated a fungus which they considered identical with the one of Lane and Medlar, while Terra, in another case in Brazil proposed for the condition the name of chromo-blastomycosis on account of the fact that the fungus gives in the tissues a distinct change of color. They classify the fungus they isolated in the genus *Acrotheca.*

Carrion, in 1933, reported a case from Puerto Rico. Several other cases of chromomycosis have since been reported in the United States (notably in Texas, St. Louis, Missouri and North Carolina) and other cases have been reported in Uruguay, Argentina, Guatemala and the Dominican Republic, as well as in Japan, Java, and Africa.*

Carrion (1940) has found other cases in Puerto Rico and has collected and compared a number of cultures. He believes that at least three species of fungi have been isolated from the different lesions: *Hormodendrum pedrosoi*, *Hormodendrum compactum*, and *Phialophora verrucosa.* Conant has studied the genus *Phialophora* in the United States and considers the fungus isolated from a case in Texas as *P. verrucosa*, while Moore and Almeida, who have studied the disease in South America and the United States, recognize as causative, species of *Acrotheca*, *Phialophora*, *Hormodendrum*, and possibly *Trichosporium.*

Weidman (1937) points out the organisms isolated from cases of chromomycosis are only mildly pathogenic for laboratory animals. Gomes 1938 reported he was able to infect guinea pigs, rats and rabbits with the organism he studied. Brumpt, and also Negroni, report the species *Fonsecaea pedrosoi* as the most common etiological agent. Brumpt originally described this species as a species of *Trichosporium.* It was first cultivated by Pedroso in 1913. Brumpt (1936) lists the species isolated in Africa as *H. algeriensis*, *H. langeroni*, and *H. rossicum* in ulcerative lesions, and *H. fontoynonti* in the squamous dermatomycosis called by Fontoymont and Carongeau "hodi-potsy."

* Simon, Harington & Barnetson (1943) have reported 6 cases occurring in the Union of South Africa. From 2 of these the causative fungus was isolated, one had the characters of *Hormodendrum pedrosi*, the other awaits classification.

The clinical descriptions in the different cases as described, vary greatly. Moore and Mapother (1940) report a case in a man aged 67, the lesion being confined to the face and consisting of a single discrete elevated pinkish patch measuring 4–5 cm. and elevated about 0.5 cm. It was firm and had a pearly appearance. The organism was found on section. Also a comparison of the lesions in Medlar and Lane's case with some of the cases reported in South America, shows very little clinical resemblance between them. Some of the cases have been reported as verrucus dermatitis and others referred to as "Mossy foot."

Thomas (1910) in Manaos described a condition which he named "mossy foot," and the following year Breinl, in Australia, also used this term to refer to a verrucous condition of the lower legs. No fungi were reported from the cases. The writer studied a case diagnosed as "mossy foot" in Manaos in 1928 but was unable to find any fungi in the lesions, either in the study of films or in the histological examination or by cultures. The term "mossy foot" is evidently an inclusive one and different cases of verrucous dermatitis may have a different etiology. In the author's case, Staphylococcus albus was isolated from the verrucous non-ulcerative lesions and in stained sections of the tissues large masses of cocci closely placed were found in spaces between the coarse connective tissue fibers in the corium. Apparently the organism had a very low grade of virulence. Other cases described as "mossy foot" have apparently been cases ot tuberculosis verrucosa cutis. The condition also occurs sometimes in filarial elephantiasis with secondary bacterial infection with cocci.

Loenthal (1934) was convinced that his cases from Uganda were different, being in fact elephantiasis with verrucous lymphatic dermatitis, which was regarded as due to lymphostasis. There was first velvety skin from chronic oedema, then verrucous papillation with horny filiform papillae and finally a stage of ulceration with sodden, offensive scaling and crusting. He studied 11 cases. No cause for the oedema could be found in 8. An illustration he publishes of the lesions of the foot is typical of dermatitis verrucosa or of the cases referred to as "mossy foot." Four cases were carefully examined for the presence of fungi by Hennesy. Slides made from fresh and macerated skin were negative as were the cultures. The same negative result was obtained in two cases with early velvet skin lesions. Sections were made and carefully examined for the presence of fungal elements. None were found. The treatment with Bayer 205 of four cases was without result. As the condition improved by careful bandaging and pressure, the name lymphostatic verrucosis was proposed. He points out that many of the cases reported as dermatitis verrucosa belong to an entirely separate disease from the "mossy foot" described by Thomas and from that seen at times in Africa which is probably a form of cutaneous elephantiasis.

Treatment.—Cases of Chromoblastomycosis in the United States have sometimes responded to iodide therapy but Carrion reports that in Puerto Rico they have been difficult to cure. The condition usually remains localized but one case has been reported with metastatic lesions. Emmons, Hailey and Hailey (1941) have reported the cure of one man after 3 months treatment by two exposures to x-rays a fortnight apart, followed by iodide of potash increased from 30 to 50 minims three times a day. The man was subsequently killed in an accident so that prolonged observation was impossible

Visceral Mycoses.—The invasion of the viscera by fungi has already been discussed under the different mycological infections. Pulmonary infection has been especially emphasized in *Blastomycosis* and *Coccidioidal granuloma* due to *Coccidium immitis* and *Cryptococcus gilchristi*, as well as in *Actinomyces*. In addition, Castellani particularly, has reported pulmonary infections with species of *Aspergillus* and *Penicillium*, as well as with *Monilia*, as a cause of broncho-moniliasis. In some of these cases, which resemble pulmonary tuberculosis but in which no tubercle bacilli have been found, it is nevertheless suggested that the fungus may represent a secondary infection.

At one period much attention was called, as in North Africa (Algeria) to a form of splenic mycosis. This was reported upon by Pinoy and Nanta (1927). In a series of cases the spleen was said to present characteristic lesions which could be observed with the naked eye and consisted of nodules 1–2 mm. in diameter, of the color of iron rust. In later papers they reported that these enlarged spleens were infected with a fungus which they first classified as *Sterigmatocystis nidulans*. Later Pinoy (1928) classified this fungus as a new species, *Aspergillus nantae*. Emile- Weil and other investigators confirmed these results and reported that this fungus infection of the spleen was also found in France. A large number of papers were shortly afterwards published, all confirming these results.

Oberling (1928) in reinvestigating his collection of 200 spleens obtained by operation or autopsy reported that 24 of them were found to show mycotic infection and contained the characteristic nodules which had been reported to be of mycotic origin by Nanta and others. Later Langeron (1938), after reviewing the literature and studying certain cultures isolated from cases of so-called splenic mycosis, concluded that there was no justification for considering that there is a mycotic form of splenomegaly. He believed that the fungi obtained in cultures from such spleens were accidental contaminations or non-pathogenic forms and that the structures described as mycelial in character were due to pathological changes in fibrin and collagen in haemorrhagic areas. Fonseca and Leao (1928), in Brazil, McNee (1929) and the writer after further study of the question were able to support the views of Langeron.

McNee, in a most careful study of the etiology and pathology of forms of splenomegaly occurring in Great Britain noted the presence of typical fibrotic nodules in one type of splenomegaly. In these he confirmed the presence of abundant calcium in addition to iron and believed that what had been described by others as fructification organs of the fungus were simply small, round, often double contoured masses of calcium. He also observed peculiar, light-green or almost colorless crystals in the nodules and the small crystals were often joined together in a way resembling the segments of bamboo canes. He favored the view that they were composed of phosphate of iron.

The writer has pointed out that in warm countries, as Africa, in instances in which autopsies have not been promptly performed, there is

the possibility that fungi present in the intestine may pass through the intestinal wall and invade other parts of the body, as the spleen. Such secondary infection with a fungus was demonstrated in at least 2 instances in autopsies upon wild animals.

METHODS OF EXAMINATION FOR FUNGI

Similar methods apply in the study of pathogenic fungi and bacteria, the objective being the separation of species or varieties either by isolation of pure cultures or the observation of pathological effects in animals.

As a rule the growth and appearance of colonies of fungi are more easily observed than are those of bacteria, and the morphology more characteristic microscopically. In the study of culture plates we necessarily become familiar with a great number of mould contaminants which we readily recognize at a glance. Castellani has attached great importance to fermentation reactions, but it is generally recognized by bacteriologists that many factors make such methods questionable in species determination. In scrapings from the skin, pus from discharges, sputum, faeces, vaginal discharges or various exudates, the standard practice is to mount in a 5 to 10 per cent solution of caustic potash. For dried scales and hairs, strengths of 20 to 30 per cent are used. Artifacts resembling spores or mycelium are confusing in caustic potash mounts. One should familiarize himself with such artifacts in normal skin preparations. For pus, sputum, empyema fluid, or various exudates and discharges, mounting in Lugol's solution is desirable.

Tribondeau's method is to treat the scales with ether, then with alcohol, and finally with water. Next put the sediment (it is convenient to use a centrifuge) in a drop of caustic soda solution. Cover with a cover glass, and after the preparation has stood about an hour run glycerin under the cover glass.

A very satisfactory method is to scrape the scales with a small scalpel, and smear out the material so obtained in a loopful of white of egg or blood serum on a glass slide. By scraping vigorously the serum may be obtained from the patient. After the smear has dried, treat it with alcohol and ether to get rid of the fat. It may then be stained with Wright's stain or by Gram's method. The ordinary Gram method may be used, or the decolorizing may be done with aniline oil, observir g the decolorization under the low power of the microscope.

Yeasts are best examined in hanging drop on a plain slide with vaselined ring.

An excellent way to examine many common moulds is to seize some of the projecting sporangia from the surface of a plate with forceps and mount in liquid petrolatum. Moulds in scales from skin or from infections of various mites or insects will show a growth in this medium when mounted on a slide and covered with a cover glass. The mycelium grows out from the body of the arthropod.

For the microscopic study of moulds it is well to clear and mount them in lactophenol (carbolic acid, 20 cc.; lactic acid, 20 cc.; glycerin, 40 cc.; water, 20 cc.). This may be tinted with some dye, as aniline blue. The above is Amann's formula.

Dodge recommends a 1 per cent aqueous solution of cotton-blue, a drop of which is placed on a slide and this is inoculated with the fungus material. A coverslip is applied and then plain lactophenol is drawn under the coverslip. A piece of filter paper at one side of the mount absorbs the aqueous solution and draws in the lactophenol drop on the other side of the square coverslip. The supravital blood staining method is of value in the study of pus, sputum or exudates containing fungi.

CULTIVATION OF FUNGI

Moulds grow well on media with an acid reaction, so that by adjusting the reaction to +2, or even higher, we permit the growth of the fungi, but inhibit bacterial development.

Glycerin agar, bread paste, or potato media are all suitable, but the standard media are those of Sabouraud:

Conservation medium (for preserving stock cultures).

	Cm.
Peptone	30.0
Agar (shred)	15.0
Tap water	1000.0

Differentiation media (two of these are used—a maltose medium and a glucose medium).

	Gm.
Maltose	40.0
Peptone	10.0
Agar (shred)	15.0
Tap water	1000.0

The glucose medium is made by substituting glucose for maltose in the above formula.

In each case the ingredients are added to the water and all placed in a cold autoclave and the pressure allowed to rise in both outer and inner jacket simultaneously until it has reached 15 pounds. The autoclave is then shut off and allowed to cool down slowly. When autoclave has cooled, the media is filtered through cotton, tubed, and then sterilized the same as above. Upon removal from the autoclave, the tubes are slanted and allowed to cool in this slanting position.

The media is not titrated or the hydrogen-ion concentration adjusted in any way, Sabouraud claiming that the addition of either acid or alkali spoils the media.

Some mycologists claim that the Sabouraud medium contains too much sugar and that this interferes with growth and morphology. The monosaccharides seem to be more objectionable than the polysaccharides. Besides potato slants, such solid media may be made from carrots in particular, but any fruit or vegetable may be similarly prepared. Some use slices of raw fruits or vegetables, deposited in moist-chamber Petri dishes. Asepsis must be rigidly observed in making the slices of raw fruits or vegetables. Mushrooms have been recommended for the study of the dermatophytes. Horse manure is often used for the study of mycelial (not yeast) growth. It should be as fresh as possible and thoroughly sterilized.

Carrot agar is used by many: Carrot, 500; agar, 20; peptone 10, and water to make a litre. Mushroom agar may be tried. Brain media have a distinct value. The Digestive Ferments Company sell prepared media, which have an advantage in standardization (comparison of culture results from different laboratories).

Before inoculating media with moulds, some recommend placing the material in 60% alcohol for one or two hours to kill the bacteria. The moulds withstand such treatment.

In cultivating moulds, small Erlenmeyer flasks, containing about ¼ in. of media on the bottom, will be found suitable for the development of the colonies. In order to isolate the mould we may take the hair or scales on a sterile slide and cut them into small fragments with a sterile knife. Then moisten a platinum loop from the surface of an agar slant, touch a fragment with the loop, and when it adheres transfer it to the agar slant. Make four or five inoculations on the surface, and from suitable growth, after four to seven days, inoculate the medium in the Erlenmeyer flask.

Plaut recommends: Place the mould material between two sterile glass slides. Seal one edge with wax and place the preparation in a moist chamber for four to seven days. From the fungus growth developing inoculate the medium in the Erlenmeyer flask. A Petri dish containing several layers of thoroughly moistened filter paper in top and bottom makes a satisfactory moist chamber.

Hanging Block Cultures.—One of the best methods of identification of moulds is to fill the concavity of a hollow slide, which has been flamed for sterilization, with melted

Sabouraud agar or other media suitable for moulds. The surface is then inoculated with material from the colony to be studied and a flamed (sterile) cover glass applied. In a similar method, which was devised for the study of bacterial cultures, Hill used 1 cm. squares of agar, cut out from sheets made by pouring melted agar into Petri dishes. Another method is to let a large drop of melted agar spread over a sterile cover glass and then inoculate the film of medium and adjust over a concave slide. These methods are excellent for bringing out the mode of fructification of moulds which can then be studied satisfactorily with high powers.

For the study of the morphology of *Monilia* in cultures, Boggs used stab cultures in 15% gelatin. The growth in the tube was hardened in 10% formalin, the glass cracked off and sections of the gelatin column cut across at any desired level. These blocks were sectioned with the freezing microtome; stained in dilute aqueous fuchsin (1 to 30) for several hours; then differentiated in saturated solution of citric acid until nearly decolorized. The sections were floated on slides, air-dried without blotting, cleared in xyol and mounted in balsam.

For staining fungi in sections of tissue, Busse recommends the following method: 1. Haematoxylin, 10 to 15 minutes; then wash in tap water. 2. Carbol fuchsin (1 to 20), 30 minutes or over night. Decolorize in alcohol for a few minutes, then pass through absolute alcohol and xylol to mount in balsam. The moulds are red.

The diagnosis of the mycoses is practically always a matter for the laboratory. The main dependence is upon the microscopic method backed up by culture. Nearly every one of the parasitic moulds will grow aerobically, though most are slow growers. Most of them prefer temperatures of from 22° to 30°C. though some of the more confirmed parasites grow better at 37°. It is perhaps unnecessary to state that we should, in studying any supposed mycosis, remember the ubiquitousness of saprophytic species of fungi and that these may grow in exudates due to lesions resulting from the action of bacteria or protozoa.

Diagnosis by Antibodies.—The attempt to diagnose a mycosis by the demonstration of antibodies is regarded by many as unsatisfactory. Some of the moulds which produce deep-seated or generalized infections may produce antibodies (agglutinins, precipitins, opsonins or mycolysins) but it is unlikely that those which grow in the upper layers of the skin (away from the superficial blood vessels) can do this. The chronicity of most of the mycoses would seem to lend support to the belief that antibodies are not produced. Also, the ease of microscopic diagnosis makes the demonstration of antibodies for this purpose usually unnecessary.

However, a number of antigens have been prepared commercially and placed on sale for diagnosis by intracutaneous reactions. Lewis (1941) emphasizes that oidiomycin is of no value as a diagnostic aid, since reactions following its administration are too frequent when there is no clinical history or evidence of moniliasis, and the test often gives a negative reaction when the patient has an obvious monilia infection. He believes the manufacturers of the commercial product oidiomycin should withdraw the vaccine from the market, since it is not of any importance in diagnosis.

Some investigators, as Jacobson and Smith (1941), believe coccidioidin is of value in diagnosis. Normal individuals, however, some times react to it.

Martin and Smith (1939) report that antibodies can be found in the sera of patients heavily infected with *Blastomyces* dermatitidis. A positive complement fixation test performed with a saline solution of *Blasto-*

myces, of a 1:4 dilution of the patient's serum, is diagnostic of the disease, blastomycosis. However, they state a negative complement fixation test does not exclude the infection.

Dermatids.—In recent years a number of dermatologists have reported the appearance of lesions of the skin resulting from an allergic condition and have termed such lesions "ids." Allergy is said to be the *sine qua non* of their existence. Thus Sutton (1939) points out that during the existence of a trichophytid the trichophytin reaction becomes positive. The dermatophytids are fungus-free lesions. When they occur, they are regarded as the result of hypersensitivity of the skin to fungus products. Thus it is believed that fungus-free lesions on the hands may be an allergic response and occur as the result of an infection with the fungus in lesions of the feet. A number of dermatologists have therefore employed inoculations of trichophytin for the diagnosis of the infection. However, in recent years a positive reaction has been demonstrated to be of little value in many cases, since when a positive reaction has occurred it has sometimes been impossible to demonstrate infection with a fungus. Lewis, Stoval and Almon believe that it may be of value sometimes in a negative way in excluding trichophyton infection.

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Chapter XLII

POISONOUS PLANTS

Practically every medicinal plant mentioned in the pharmacopoeias of the world grows naturally, or can be grown, in different tropical countries, owing to the diversified climates and soils which exist in a number of them. Many of the tropical plants contain powerful and toxic principles and these, when introduced into the body of man or other animals, may give rise to serious impairment of bodily functions, or even produce death. While the majority of the poisonous plants of the tropics which are recognized have been used as medicinal agents, others have been employed for criminal purposes. Many of the less civilized tribes use such poisons not only to fight their enemies, but to kill game and fish for food.

The natives of tropical countries possess considerable and at times a surprising knowledge of the effects of many poisonous plants, while among the more civilized individuals poisoning by accident, ignorance or intention is still fairly common. However, the number of plants by which man is commonly poisoned is not very large.

Livestock may be poisoned by a much larger number, although by instinct such animals often avoid the most toxic plants unless forced by hunger to eat them. The loss from poisoning among cattle is unquestionably very large in many countries. No figures of value are available in the tropics, but in Montana and Colorado it has been estimated that the loss to livestock by plant poisoning is in the neighborhood of $200,000,000 annually.

The "alkali disease" predominating in South Dakota and an affection known as "blind staggers" in cattle and horses, predominating in Wyoming, develop from the animals eating small amounts of selenium-bearing vegetation over a long period. However, in "blind staggers" of the acute type the symptoms develop after feeding for a short time on plants containing much larger amounts of selenium. Extensive literature on the subject of selenium poisoning has accumulated during the past 10 years. Anyone interested in the subject may consult the articles of Trelease and Martin (1936), Beath (1937), and Moxon (1937).

The chemical constituents of plants which are responsible for their toxic effects may be classified in a number of groups.

1. In which the substances are vegetable bases which include the amines and alkaloids. In many instances these are of an intensely poisonous nature. Some of the amines give a foetid odor to the plant, and to some of the mushrooms their poisonous characteristics, while the alkaloids as a rule give a bitter taste to plants in which they occur naturally. This in itself is frequently a protection to man and also livestock, which may come into contact with them. A great many medicinal drugs owe their

valuable properties to these alkaloids, such as strychnine from nux vomica; aconitine from the different species of *Aconitum;* atropine and allied alkaloids from belladonna; morphine from the poppy; and nicotine from tobacco.

2. Another class of poisonous substances found in plants are glucosides. They form a much larger group and are of more common occurrence than alkaloids. Many are intensely poisonous, but others are non-toxic. They also generally have a bitter taste and are employed in many of the plant extracts used in medicine. Common examples of toxic glucosides are nerioside and cymarin, found in the Oleander family (*Apocynaceae*, or Dog-bane family); and Digitalis (*Scrophulariaceae;* the Figwort family). In some instances, as in the leaves of the foxglove, the plant may contain several glucosides, of which digitoxin, digitalin, and digitonin are among the most active and toxic. Horses and cattle have been frequently poisoned by eating the leaves of foxglove, as well as of species of Indian or American hemp of the Dogbane family.

Another group of glucosides important as poisons are the cyanogenetic glucosides which contain hydrocyanic acid which may be liberated by enzymes occurring in the plants themselves. These enzymes may liberate sufficient quantities of hydrocyanic acid in the animal body to produce fatal results. A common substance of this class is that occurring in bitter almonds (amygdalin). They also occur in bitter cassava (*Manihot*) and a number of the members of the tea and rose families, a number of the wild cherries and prunes being a common source of poisoning (Couch, 1934).

One group of glucosides (saponins) when shaken with water produce a soapy foam. They occur in a very large number of plants which are dispersed in more than 50 different families. They are particularly poisonous to certain of the lower animals, for example fishes, frogs and insects. Some of them are especially employed by the natives in poisoning fish. One part in 200,000 or more parts of water may be fatal to the fish, in which they produce paralysis of the respiratory organs. In animals, when taken by mouth, they produce gastro-intestinal irritation, vomiting and diarrhoea, and they cause haemolysis when they come into contact with blood. Other common examples are species of the *Sapindaceae* (Soapberry family), the soap nut, soap bark, and soap root.

3. A third group of poisons consists of essential or volatile oils which often give characteristic odors to the plants. Many of these are insect repellant for this reason, but in some instances, in addition, they are insecticidal. Common examples are those which are found in absinth (from wormwood, *Absinthium*) which produces convulsions by its action on the nervous system, or in eucalyptus, with a camphor-like odor and to some extent insect repellant. Others occur in the Pine family, the English and Japanese yew being particularly poisonous when the wood bark and leaves and the seeds are eaten by animals. However, the red pulp of the berry seems to be harmless. An important essential oil produced in the mustard seed by action of an enzyme, or in the seeds of *Argemone* with which it is adulterated, has apparently given rise to large numbers of cases of epidemic dropsy in India.

As striking examples of the vegetable insecticides may be mentioned pyrethrum, obtained from the flowers and roots of *Chrysanthemum cinerariaefolium*, and derris powder from the roots of several species of the genus *Derris*. The latter is used also especially in fish poisoning, and in New Guinea derris root is commonly employed for suicide.

4. Toxic substances known as toxalbumins occur, for example, in species of *Croton*, *Ricinus* and *Abrus*. There are especially blood toxins and may give rise to antitoxins on intravenous injection. They are responsible at times for considerable losses in livestock and more rarely cause poisoning in man. Animals, however, may become more or less immune if given small and increasing doses of these substances in their food. Other species of Euphorbiaceous shrubs, as of the genus *Curcas* or *Jatropha*, which produce nuts somewhat resembling sweet almonds, contain phytotoxins, as curcin, and not infrequently give rise to poisoning in man.

5. Another group of poisonous substances may be classified as resins (before extraction) occurring, for example, in species of the Berberidaceae (barberry family) especially of the genus *Podophyllum* (mandrake) or in the fruit of *Citrullus colocynthis*, both of

which are sometimes employed as purgatives. Other examples are found in the species of the Cashew family, including *Rhus toxicodendrum*. Highly toxic substances, as andromedotoxin, are found in species of the genera *Rhododendron* or *Kalmia*, and picrotoxin, a convulsive poison resembling strychnine in its action, is found in *Anamirta cocculus* or *Cocculus indicus*.

The above examples should give some idea of the diversity of the more common toxic chemical substances so widely distributed. Obviously only the more important of these poisonous plants and the disturbances they produce which the tropical practitioner is likely to observe can be discussed in this text book.

Arrow Poisons.—Many primitive people add to the wound effect of their arrows, that of poison. Although animal secretions, particularly snake venoms, are used, they are inferior in effect to the vegetable poisons. In some arrow poisons snake venom is combined with the plant extract, but as the users often treat the snake venom in such a way as to destroy the toxins, the effect must be due in such cases entirely to the vegetable poison. Material of bacterial nature has also been used, particularly the tetanus bacillus, but most of the potent arrow poisons are vegetal.

Strophanthus is one of the most important of the *Apocynaceae*. Various species of this genus are used by African tribes, extracts being prepared from the seeds and often mixed with heads of snakes. At least two species are found in Liberia,—*S. sarmentosus* and *S. gratus*. They grow in bushes which produce striking pink, pentacle-like flowers. This poison, which has been used especially for poisoning arrows, is obtained by cooking the seeds in water and letting them evaporate to a syrupy, tarry mass. A small amount of vegetable resin is sometimes added. The action of the poison is known to the medicine men and it is said to be used chiefly by them. Strophanthin is the active principle, but the species *S. hispidus* contains another substance known as pseudostrophanthin, which is more toxic to the heart muscle. After poisoning, the victim's breathing and pulse become gradually slower until the heart beats suddenly cease. Frequently a convulsion occurs before death, the heart being arrested in systole. In smaller doses the drug acts as a circulatory stimulant.

Acocanthera is another important genus of the Apocynaceae, various species of which furnish a powerful poison. It is prepared by mixing a decoction of the wood or roots and evaporating over the fire until a syrupy consistency is attained.* The gall bladder of an animal is often added to the mixture, if it is to be painted over the heads of arrows.

The poison from the species *A. venenata* known as ouabain contains both an amorphous and a crystalline glucoside related to those in digitalis. It produces very rapid death, which occurs after rapid, irregular heart beats, rapid respirations and convulsions. Sometimes there is a great loss of muscular power.

The sap and seeds of other species, as *Cerbera odollam* and *Thevetia nerifolia* contain a glucoside, "thevetin," which causes death from heart failure in 12–15 hours.

* The species *A. spectabilis* is known as Bushman's or Hottentot's Poison.

Hyoscyamus falezlez, one of the Solanaceae, is another poison employed by some of the natives in the interior of Africa and the Tuaregs of the Sahara. It produces symptoms like those produced by ouabain, but it is not so powerful a poison, though it contains hyoscyamine and scopolamine.

Strychnos.—The principal arrow poison of the Amazon river tribes is curare, made by extracting the bark of various *Strychnos* species. Dr. A. Hamilton Rice in his studies in Amazonia found that curari is prepared from the cortex of a vine called Itary-cipo (genus *Strychnos* such as *S. toxifera*), the sheath or rind of which is macerated and triturated, afterwards boiled with a small amount of water, put into a tipiti press (made from the jacitara palm, *Desmoncus macroacanthus*, Martius), and allowed to exude slowly; then boiled to the consistency of an unguent, and stored in little pots. Into this curari are dipped the tips of the slender darts (obtained from the footstalks of the pataua palm, *Oenocarpus bataua*, Martius) which are used with the blow-pipes (zarabatana), last named made from the smaller paxiuba palm (paxiuba miri, *Iriartea setigera*, Martius).* Curari contains 2 alkaloids, curarine and curine. The former arrests voluntary movements, by interrupting connection between the peripheral nerves and the muscles, and the animal lies helpless on the ground, while the latter paralyzes the heart. Certain Malay tribes use poisons from this genus, but their arrow poisons seem to contain strychnine and brucine as well as curarine, so that in animals wounded by such poisoned darts we have convulsive phenomena, as well as the action on the motor end plates. In India, the species *Strychnos colombrina* is used also in homicidal and suicidal cases and is used for killing dogs, rodents, etc. It is also used as a fish poison. Other poisons used by certain Himalayan tribes have aconite as a base.

The sap of *Antiaris toxicaria* is also used as an arrow poison in India and is a powerful cardiac poison (Chopra, 1940).

Atriplicism.—A disease of North China supposed to be due to the toxic properties of a weed, *Atriplex littoralis*, which grows in gardens around Pekin, is possibly caused by a small insect often found on the weed, as it is claimed the weed will not cause disease if well washed before eating. It is only in times of famine that the weed is eaten, and then only by the very poor. About 15 hours after ingestion there appears itching of the fingers, quickly followed by swelling and discoloration. This swelling extends up the backs of the hands and outer surface of the forearms. The face also becomes swollen so that the eyelids may be closed, and the nose becomes cyanosed and cold. The swollen parts may ultimately develop blisters and ulcers. Later the finger tips may become gangrenous, the face and eyelids cyanotic and oedematous. Sometimes the cases resemble Raynaud's disease. Uyky has recently described cases with these symptoms after eating leaves of this plant and he believes that the cutaneous lesions may be ascribed to a light sensitive dermatitis. Some

* Wintersteiner and Dutcher (1942) have obtained Curare in crystalline form from the vine *Chondodendren tomentosum* (Science 1942).

species of *Atriplex* are said sometimes to become poisonous through the absorption of selenium from the soil (Muenscher, 1939).

Yang (1940) points out there is much that is obscure in regard to this subject. He observed that it occurs in those eating the food who have had no part in gathering it and hence that it is not due to the small greenish-yellow mite that is often found on the plant. The symptoms did not arise in those who had eaten atriplex unless they exposed themselves to bright sunlight and since the lesions appeared only on exposed parts he thinks the immediate cause is irritation due to the sun's rays, though the question of sensitization to sunlight by ingestion of the herb needs consideration and study.

Cannabis indica occurs especially in India, Persia and Arabia. It is the cause of a pernicious drug addiction in Central Asia and the plant is generally called Indian hemp. In India the forms of the drug generally used are "gangah," the dried flowering tops, which is smoked, mixed with tobacco; "bhang," a mixture of the dried leaves and capsule, which is made into decoctions and is the cheapest form of the drug; and "charas," the resinous exudate obtained from the cut female heads of the plant. This is the most expensive and most concentrated of the preparations. In Arabia a confection is made from charas and is known as "hashish." It is sometimes mixed with extracts of different *Solanaceae* such as datura and nux vomica and in this form is said to be taken daily by millions of the inhabitants of Africa and Asia, although stringent regulations against its sale have been taken in some localities. The drug gives a feeling of well being, followed by hallucinations of sight and hearing—often of sensual character. This is followed by dimness of vision, drowsiness and stupor. Addicts may become insane. Chopra says that in India *Cannabis indica* is often spread upon the beds to drive away bugs and is also used as a fish poison in Bengal.

Cannabis Sativa.—*Marihuana*, is the name given in Mexico and the United States to the flowering tops of this hemp plant, a member of the flax family widely cultivated in the United States and elsewhere for its fibre. It also grows wild as a weed.

The flowering tops, especially those from the pistillate (female) plant, are smoked in India under the name "gangah." In the United States, hemp cigarettes bear various names besides marihuana,—as reefers, muggles, the weed, etc. In some instances, an extract is made of the tops and used to impregnate tobacco cigarettes.

The use of marihuana seems frequent in underworld resorts and has been reported among the better social classes. The dangers attending use of the drug, especially by young people in the public schools, was first emphasized in New Orleans about 1926; and a Federal law making the use of Cannabis illegal was passed in 1937.

Heroin or other derivatives of opium have been added to the marihuana in order to create opium addiction; for apparently true addiction does not follow the use of cannabis, there not being clearly demonstrable tolerance-increase or withdrawal symptoms.

The intoxication, which may arise from the smoking of a single cigarette and may come on in an hour or so, is characterized by excitement, mental confusion, talkativeness, and often spells of hysterical laughter. Visual hallucinations and sexual illusions also are features of the intoxication. Many of the cases treated in hospitals are neurotic, that type of personality being given to use of the drug for the pleasurable phases of its action. While euphoria is experienced, there is at the same time an anxiety complex which may lead to ideas of suicide.

Many cases are cited of homicidal attacks by persons when under the influence of marihuana. Bromberg, however, in reporting his study of this addiction at Bellevue Hospital, questions whether it predisposes to crime, noting that no cases of murder or sexual crime were established as due to marihuana in 67 trials in the U. S. County Court of General Sessions. Nevertheless, there is general agreement that marihuana cigarette smoking brings about weakening of restraint and impairment of judgment; and it would seem that the excitation of sexual illusions might well lead to sex crimes. In his book, "Marihuana" (1938), Walton states: "The situation is of the utmost gravity and is one which calls for drastic measures of eradication."

Favism.—This is a disease caused by inhaling pollen from the flowers of the bean plant or by eating the bean (*Vicia faba*)—most frequent in Italy and especially southern Sicily. Heredity seems to play a part, some families giving a history of favism over many generations. (Idiosyncrasy.) Ingestion of raw beans is more apt to cause it than eating cooked beans. About half of the cases are due to exposure to blooming plants. There seems to be no relation between the amount of bean eaten and the severity of the symptoms. This, taken in connection with the hypersensitiveness to the bloom, would surely indicate some form of allergy. About 8 per cent of the cases are fatal. McCrae and Ullery (1933) reported a case in Philadelphia. The patient, an Italian, gave a history of attacks from pea blooms when living in Sicily. Following a

hearty meal of beans he began to feel very ill and two hours later on voiding urine, noticed that it was black. He was of the opinion that the beans he had eaten were from Sicily. Five days later he was admitted to hospital showing ashen gray color of facies and pallor of mucous membranes which was accompanied by jaundice. There was some fever and the urine was absolutely black (haemoglobinuria) and showed many granular casts. Red cells were about 1,400,000 and the haemoglobin 38 per cent. The leucocyte count was 19,300 with 73 per cent polymorphonuclears. Reticulocytes were about 14 per cent. There was about 11 per cent of erythroblasts and rather marked anisocytosis. Blood urea nitrogen was 37. Paroxysmal haemoglobinaemia was excluded by the Donath-Landsteiner test. (The patient had a positive Wassermann reaction.) A skin test showed allergy to an extract of the beans eaten. This case was apparently the first to be reported in English or American literature. On account of the great number of Italians living in the United States it must be that the allergy described above is not frequent. In Italy it is noted that the attack comes on shortly after exposure with an irregular fever and haemoglobinuria. The sudden and great fall of red cells may cause death in a very short time. When the patient does not die, recovery takes place satisfactorily. Epinephrin and blood transfusions are to be considered, in treatment. Muensch does not list any species of *Vicia* native in the United States, so that the beans eaten by the different patients were probably imported. In India, *Vicia sativa* has been shown to contain bases with alkaloidal properties which have been named "vicine" and "divicine." Robinson (1941) has observed 6 cases in Palestine, in all following the eating of the broad beans, acute haemolytic anaemia was present. The first symptoms were vomiting and diarrhoea. The skin turned pale grey. The urine was reddish brown. The cases were first mistaken for those of Lederer's anaemia. The disease is especially common in Sardinia and Sicily. The morbidity rate in Sardinia is as high as 5.17% with a case mortality rate of 8%.

Kava or Yangona.—An intoxicating (non-alcoholic) drink is made from the roots or leaves of the pepper plant, *Piper methysticum*, and is a ceremonial beverage in many of the islands of the South Pacific. The parts of the plant were first chewed by young girls who have good teeth and good health, and the masticated material is put in a bowl and treated with coconut milk. A sort of quiet, drowsy intoxication, with weakness of the legs, results in those not habituated. In the chronic intoxication a condition of debility results and a marked roughness of the skin is said to develop.

Lathyrism is a disease characterized by nervous manifestations, a form of spastic paraplegia, and there are symptoms of weakness and muscular pains without psychical disturbances. It is common in Abyssinia, Algeria and India. It has been believed to be due to eating, in times of scarcity of bread made from the flour of the chick-pea, *Lathyrus sativus*, or other species of vetches. The disease comes on insidiously with pains in the back and weakness of the legs. As the affection develops, the legs are dragged along with great effort, and there is a tendency to fall. Wasting of the leg muscles is common. Reflexes are exaggerated. Incontinence of urine and loss of sexual power are important symptoms. The upper extremities are only rarely involved. There is no mental or cardiac involvement. The disease runs a very chronic course but is rarely fatal. A deficiency in vitamin A has been suggested as a factor in the production of the disease. In India, this plant is known as *Khesari dal.* It is an important article of diet for both man and animals in most parts of India, and Chopra (1940) emphasizes that a large number of cases of poisoning are due to it. He says examples of lathyrism in man in the form of spastic paralysis are commonly seen every day in the streets of Calcutta. While

moderate amounts of this pulse can be taken with impunity, when large amounts are taken, especially to the exclusion of other foods, the unfavorable symptoms develop. Minchin (1940) has studied a series of 21 cases between 19–45 years of age, all of whom but one were males, with symp-

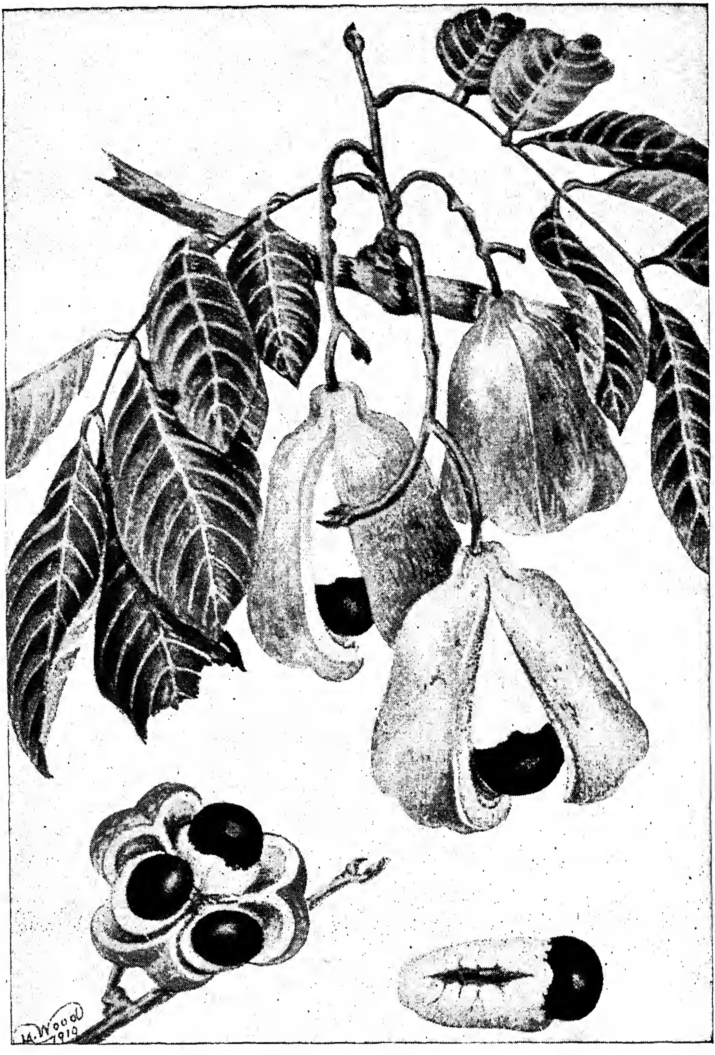

FIG. 268.—*Blighia Sapida* Koen "Akee."

toms of spastic paraplegia with retention of abdominal and cremastaric reflexes and no sensory changes. They seemed clearly to be cases of primary lateral sclerosis and by elimination, the syndrome was seen to be identical with that of lathyrism. He, however, says that *Lathyrus sativus* is not consumed by the inhabitants of South India, but that the

diets were deficient in vitamins and proteins. *Lathyrus sativus* grains are rich in proteins but deficient in tryptophan. In his cases, he suggests the condition may be due to tryptophan deficiency and that hence symptoms of this nature may occur in the absence of this vetch (see Chap. XXXII on Vitamins). Acton and Chopra concluded that lathyrism is not due to *Lathyrus sativus* but to the contaminating weed *Vicia sativa*, and that the toxic principle divicine was found in this contaminating weed. It was regarded as closely related to barbaturic acid. They believe that lathyrism occurs when the ordinary food *Khesari dahl* is contaminated with the white akti. Chopra (1936) apparently does not believe that the experimental proof of the actual factor responsible for the production of lathyrism has been demonstrated.

Milk Sickness.—Cattle eating richweed (white snakeroot, *Eupatorium ageratoides* or *Urticae folium*) in the eastern United States, or rayless goldenrod in Texas (*Aplopappus heterophyllus*) acquire a serious disease called *trembles*, or in some instances "alkali disease" or "milk sickness." In man there are observed anorexia, nausea and vomiting, which prevent the taking of food and water, and soon bring about an acidosis characterized by a high mortality. The later symptoms are subnormal temperature, extremely low blood pressure, presence of diacetic acid in the urine, and of the odor of acetone in the breath and urine. The blood shows a marked ketosis, a lipaemia and a hypoglycaemia. The poisonous principle of *Eupatorium* and *Aplopappus* is trematol, one of the higher alcohols and is found in the leaves and stems (Couch, 1933).

Vomiting Sickness of Jamaica, or Akee Poisoning.—This is an acute and often fatal disease common in the West Indies. It is due to eating unripe "akee," or "ackee," the local name of the fruit of *Blighia sapida*. The fully ripe, opened fruit is harmless and is a valued food. Children eating the unripe fruit, with abnormal arilli which may contain the poison, become suddenly ill in about 2 hours, with abdominal pain and vomiting. There is a period of apparent recovery, lasting a few hours, after which vomiting again begins and almost coincidentally convulsions and coma, ending generally in death. In earlier periods it was sometimes confused with yellow fever. The disease has attracted wide attention in Jamaica for many years.

Scott (1939) has studied this affection for a long period and says that according to history more than 500 persons in one island of the West Indies were carried off by it. Apparently the tree was not originally found in the West Indies, but was introduced there in 1778 from a West African slave ship. The name *akee* was given to the tree by the natives of the Gold Coast, while the local name of the fruit there is "*isin*" or "*ishin*." It was regarded as sometimes being poisonous in Africa, as a common saying reported from there was "He who eats the isin should know how to remove the poison."

There has been a great deal of discussion for many years as to the amount of vomiting sickness caused by the ingestion of the akee fruit. Scott, however, has collected very convincing evidence of a clinical, seasonal, pathological and experimental nature that the vomiting sickness may be due to poisoning by this fruit, especially when it is gathered from an injured plant, or after falling on the ground. It is said that the poisonous element in the immature and unsound fruit is soluble in water, for pot water

in which the ackees have been cooked is thought to be much more toxic than the cooked fruit itself.

Jordan and Burrows (1937) carried on an extensive study of the affection in Jamaica. They found that the seeds were the most prolific source of the poisonous substance. The inocuous nature of normal arilli was indicated by their wide consumption by the general population with no ill effects, and they were unable to detect the poisonous substance in this portion of the ackee by feeding it to cats and monkeys. But with abnormal fruits such as those which were unripe and that had hung upon a dead branch or had lain upon the ground, while some of these were not toxic, extracts of their seeds proved markedly toxic to cats. They found that the seeds and pods of both ripe and unripe ackees contained a substance which, upon ingestion, induced violent vomiting in both young cats and *Macacus rhesus* monkeys. Their evidence suggested that the ackee poison was a glucoside.

Evans and Arnold (1938) have performed careful chemical studies upon the akee fruit and have separated the constituents into saponin, fat and phytosterol, and demonstrated the toxicity of the saponin.

Scott had long ago suggested the toxic principle might be a glucoside, but merely on the ground that the poison could not be obtained from the gastric content or tissues or excreta of fatal cases and he inferred, therefore, that the toxic agent was some substance rapidly decomposed or changed on absorption. Evans and Arnold point out that cases of akee poisoning more commonly occur from December to February or March, and they have shown that in these colder months of the year the saponin content of the akee is higher and the toxicity greater. By careful tests, they have shown that the normal, naturally opened, akee is harmless, whereas the unopened fruit is highly toxic. The arillus of the unopened akee was lethal to kittens with a dose of 1.0 gram per 100 grams of kitten weight when administered intragastrically and was lethal to guinea pigs when a dose of 3.5 grams per 100 grams of guinea pig weight was given subcutaneously or intragastrically.

The toxic property is cumulative when repeated sublethal doses are given at daily intervals. The arillus of the fully opened akee is not lethal to guinea pigs. The postmortem findings in both kittens and guinea pigs indicate an active toxaemia affecting all the organs, with haemorrhages and fatty changes, chiefly in the liver and kidneys. The saponin found in the arillus of the unopened akee is strongly haemolytic, nonhaemolytic in the arillus of the fully opened akee, and only slightly haemolytic in the partly opened akee.

It seems, however, quite evident that there are many cases of individuals with symptoms of vomiting sickness in Jamaica in which the disturbances may be due to the ingestion of other irritating or even poisonous foods.

Mushroom Poisoning.—The best known edible mushrooms are (in England and the United States) the meadow mushroom, *Agaricus campester*, which grows only in open pastures and (in France and Italy) the champignon, *Marasmius oreades*. There are no criteria by means of which edible mushrooms can be distinguished from poisonous varieties.

There is a wide-spread, entirely erroneous belief that if a silver coin is put in the dish in which mushrooms are cooked, it will be tarnished if poisonous varieties are present. They can not be recognized by the taste—the most poisonous species are said to have a very agreeable flavor. In Washington an Italian officer who was regarded as an expert in the recognition of edible species, purchased in a market some mushrooms which had been collected in nearby Virginia. He breakfasted on these mushrooms and spoke of their fine flavor. In about 15 minutes he became acutely ill, developed blindness, dysphagia and convulsions and died within 24 hours. If one has not the expert knowledge required to identify the species with certainty, one should eat only mushrooms which have been passed upon by a competent (preferably official) inspection. Even in cultivated beds, poisonous species occasionally develop.

There is marked individual variation in susceptibility. In the case of a family of 6 poisoned by *Amanita nappa*, reported by Bentkowski, four died (one of whom had eaten only a mouthful); one became ill but recovered, and the sixth who had eaten heartily suffered no ill effects.

In the United States most cases of poisoning are due either to *Amanita muscaria*, the fly amanita, or to *A. phalloides*, the death cup. Both species are widely distributed and very common. One feature which helps to identify this genus is the persistence of a portion of the veil, encircling the stem a little below the cap.

The poison in *A. muscaria* is muscarine, an alkaloid related to pilocarpine. This type is distinguished by the early appearance of symptoms (within three hours), and death in the fatal cases occurs within 24 hours. There are nausea, vomiting, diarrhoea, severe abdominal pain, sweating, salivation, lachrymation, miosis, often a slow irregular pulse, and in fatal cases, convulsions and coma. Atropine is an efficient antidote, and although the symptoms are violent, the mortality is low (about 10 per cent) in properly treated cases.

The poison in *A. phalloides* is a toxin. In this type the symptoms are late in appearing (6 to 18 hours), and although the mortality is from 50 per cent to 70 per cent, death usually occurs only after 5 to 8 days. In addition to the gastrointestinal symptoms noted above, there may be great thirst, anuria, jaundice (after two or three days), cyanosis, drowsiness, delirium or coma. There is degeneration of the renal tubular epithelium and liver necrosis; and extensive degeneration of the ganglion cells of the cerebral cortex, basal ganglia, cerebellum and brain stem have been described (Vander Veer and Farley, 1935). Atropin has no effect. An antitoxin has been used in Europe with alleged good results.

Another rarer type of mushroom poisoning, resulting in an acute haemolytic anaemia, haemoglobinuria and jaundice, has been described. Recovery is the rule.

There is little information available regarding the poisonous fungi in most tropical countries. However, species of *Amanita* are not uncommon and in India at least one of these contains the poisonous principles of amanitine and muscarine.

Other known poisonous species of this genus in India are *Amanita muscaria* (fly agaric), and *A. pantheriana* (warted agaric). Still other common poisonous ones are *Stropharia semiglobata*, *Hypholoma fasciculare* and *Lactarius vellerens*. *Lepiota cristata* (crested agaric) and several other species of *Lepiota* are regarded with suspicion. Chopra points out that *Psalliota xanthoderma*, the yellow staining mushroom, has caused illness in some cases. *Volvaria gloiocephala* (the glutinous agaric) and related species have always been regarded as poisonous. However, Chopra says there is recent evidence that shows these may be eaten without ill effects. He points out that the number of species that are poisonous is comparatively few to the number eaten widely in India. He remarks that if they are first macerated in vinegar before thorough cooking and eaten with plenty of bread few are dangerously poisonous, as the poisonous principle is destroyed at 100°C.

Ergotism is another well known illustration of accidental poisoning from the ingestion of food plants, rye, or other cereals, normally wholesome but which have become contaminated with the fungus.

Plants Causing Dermatitis Venenata.—There are a great many plants in various parts of the world which cause various types of dermatitis—erythematous, vesicular, or urticarial. The best known of these plants belongs to the Rhus family. By far the most common cause of plant dermatitis in the United States is poison ivy, *Rhus toxicodendron*, and its closely related form known as poison oak. The poison sumac, *Rhus vernix*, in the northeast, and poison wood, *Metopium toxiferum*, in the extreme southeast, produce similar and often more severe dermatitis (Muenscher, 1939). For poisoning with these plants it is necessary that contact be made with the plant—the idea that a volatile principle is given off is not true. The exciting agent is toxicodendrol and it can produce dermatitis in susceptible persons in exceedingly small quantities 0.001 of a milligram).

Repeated attacks do not seem to confer an immunity. Following exposure, the skin should be washed and scrubbed with soap and water. Alcoholic solutions or oily ones spread the inflammation. Striking results have been reported following administration of poison ivy and poison oak extracts. These extracts are solutions in a vegetable oil of a substance extracted from the fresh leaves of poison ivy and poison oak. They are given intramuscularly at intervals of from 24 to 48 hours. Most plants seem more irritating when wet than when dry.

Reuter and White (1941) have studied the susceptibility to and latency of poison ivy dermatitis. A section 2 cm. square was cut from a fresh leaf and rubbed immediately, with moderate friction, for approximately 30 seconds on two skin areas; one on the flexor surface of the fore arm and the other on the lower leg. A dry dressing was applied and the subject was instructed not to wash the areas inoculated until permission was granted. Daily observations were made of the inoculated areas. Twenty of the 23 subjects gave a positive reaction consisting of erythema, papules, vesicles, sometimes with pruritis and more rarely with oedema. Of these, 15 reacted to the first exposure. The shortest period of latency was one day, the longest 18 days and the average 6 days. The duration of the reaction varied from 2 to 21 days. The cases of shortest incubation and most marked reaction were usually those of longest duration as well. There were no apparent variations according to sex, race, or site of inoculation. Two subjects who showed immunity after the second test were Jewish and fair of skin. One perspired profusely, with an otherwise normal skin. The other had a skin in no way different from the other subjects tested.

A large number of other plants are capable of causing dermatitis in man in the United States. Among these are the parsnip, *Pastinaca sativa;* lady-slippers, Cypri-

pedium spp.; spurges, Euphorbia spp.; and the cultivated primrose. Certain plants of the primrose family, as the species *Primula obconica*, are apt to cause a dermatitis, especially when the primroses are in flower. Lily rash is a dermatitis caused by handling various bulbs or stalks. Those handling the vanilla bean may suffer from an itching dermatitis. The rue group of plants also is often responsible for skin irritation.

Chittendon (1931) and Weber (1937) have made extensive studies of these and other dermatitis producing plants.

In Japan, the lacquer from *Rhus vernicifera* causes a skin oedema affecting the face and extremities, which is followed by a papular eruption.

Anacardiaceae (*Mangifera*).—Kirby Smith (1938) has called attention to the fact that a form of dermatitis, especially of the hands, neck and face, particularly of the lips, may follow eating mangoes. These symptoms and burning and itching may appear 6 to 8 hours after their ingestion. The skin or rind of the fruit, as well as the stem or sap, contain the irritating resin, and not the edible portions of the fruit. Most people realize that the rind is irritating to the mucous membranes. Some individuals are allergic to mangoes, as others are to strawberries.

Ginger Paralysis (Jake paralysis).—From February to April, 1930, attention was drawn to mysterious outbreaks of paralysis in certain parts of the United States, especially Cincinnati and Tennessee. Male adults were chiefly attacked and all gave a history of drinking Jamaica ginger one-half to 3 weeks before the attack. The most striking symptom was a flaccid paralysis of the distal muscles of the limbs without involvement of the sensory nerves except for a feeling of numbness and aching of the calf muscles preceding actual paralysis, which usually followed after 3 or 4 days. In other cases the arms later became involved. The knee jerks were usually increased; the plantar reflexes abolished. In some instances the flexor muscles were found to be weaker than the extensors and there was subjective loss of strength. Cases were later found in Oklahoma in February 1930. By the end of April over 500 cases were detected and it was later estimated that there might have been in the neighborhood of 1500 cases. Outbreaks occurred also in the middle and southwestern states. In southern California there were 125 cases, and 316 were admitted at the Cincinnati Hospital. Others were reported from a number of the southern and other central western states.

The disease was regarded as a type of polyneuritis of undetermined cause. It was suggested in Boston that the paralysis ought to be regarded as an industrial accident and the condition was ascribed by some of the patients to their work being performed on damp and cold floors or to working in drafts. Death occurred in some instances and was thought to be due to respiratory paralysis. An examination of the nervous tissues revealed degeneration of the myelin sheaths and axis cylinders of the radial, ulnar, sciatic, external popliteal and anterior and posterior tibial nerves. The process was not found to extend up to the anterior roots. Later studies estimated the number of cases that had occurred as between 10,000 and 15,000 and that the symptoms followed the use of an extract of Jamaica ginger. Children were never attacked. The cases were from 7–9 times more frequent in men than in women. The average age was 47 years. The fatality rate was not high but in some cases the disability persisted for two years or even longer.

The cause was eventually found to be due to the consumption of adulterated Jamaica ginger which contained 2 per cent of triorthocresyl phosphate (Smith, Elvove Valaer, Frazier, and Mallory). Later investi-

gations carried out showed that chickens inoculated with unadulterated Jamaica ginger remained healthy while others inoculated with the ginger containing 1.5 per cent of the phosphate developed polyneuritis after about 9 days.

Carillo and Ter Braak (1932) described an outbreak of poisoning arising from apiol and Jamaica ginger. Apiol is an alcoholic extract of the fruit of the common parsley (*Carum petroselinum* or *Apium sativum*). The drug has been used as an abortifacient and for menstrual disturbances and in malaria and contains from 28 to 50 per cent of triorthocresyl phosphoric acid. Carillo found that secondary changes might occur in the spinal cord which had not previously been noted.

Water Hemlock.—Poisoning from species of the genus *Cicuta* (water-hemlock) of the Parsley family is not uncommon in man and cattle. The poisonous property "cicutoxin" is a resinous substance found especially in the roots and root stocks. The leaves and fruits may apparently be eaten by animals without danger. Children and adults have eaten the fleshy roots, mistaking them for parsnips, artichokes or other roots, and serious or fatal results have followed. The symptoms are pain in the stomach, nausea, sometimes leading to violent vomiting, diarrhoea, dilated pupils, labored breathing, sometimes frothing at the mouth, weak and rapid pulse, and violent convulsions. In fatal cases the convulsions grow more violent until terminated by death, which results from respiratory failure. In cattle, spasmodic contractions of the diaphragm occur instead of vomiting.

The poison hemlock of the Parsley family (*Conium maculatum*) is probably the most generally known poisonous plant historically, it was said to have been administered by the Greeks to Socrates and other State prisoners. Cases of poisoning have occurred recently from accidental eating of the seeds, which have been mistaken for those of anise or eating leaves, mistaking them for parsley, or the roots for parsnips. The plant seems to be most poisonous in the spring. The symptoms in man are a general and gradual weakness of muscular power. The power of sight is often lost, but the mind usually remains clear until death ensues from the gradual paralysis of the lungs. A difference from poisoning by water-hemlock is the absence of convulsions. Obviously, in all cases of poisoning of this nature, an emetic should be administered immediately.

Mustard Oil Poisoning (Epidemic Dropsy).—Epidemic dropsy is a disease which somewhat resembles beriberi, since it is characterized by dropsy associated with cardiac symptoms but without marked paralysis or anaesthesia. It has been described in India, in Calcutta, since 1877. In 1879 an outbreak was reported in Mauritius in which one-tenth of the coolies were attacked and a large number died. In 1926 an outbreak occurred in Fiji which was confined to the Indian population. There have been other outbreaks reported in India at intervals since 1913. One of the worst was in 1934, when over 2,000 cases were observed. At the time of the outbreak in Fiji in 1926, as the disease was confined to the Indian population and none of the native Fijians, were attacked, it was suggested that the affection was due to mustard oil used in the preparation of the curries. Later Banerji and Ghosh in Bengal, and Lal, Roy and Ghosal in Calcutta, also supported this idea. In experiments among

volunteer convicts in the Calcutta jail, 6 persons who were given suspected oil developed characteristic symptoms after 5 or 6 days, while the controls remained healthy.

Lal and Roy, in Calcutta, also conducted feeding experiments on 12 healthy young subjects and on the fifth day symptoms were noted, consisting of fever and oedema of the legs. Hawes believed the essential substance in mustard oil poisoning is allyl-isothiocyanate and believes changes in the oil take place when it is cooked at a high temperature. Chopra and Badhwar (1940) point out that in some of the epidemics the mustard oil was adulterated with *katakar* oil, from seeds of *Argemone mexicana*, the Mexican poppy or *shialkata*. Experimental work on human volunteers showed that food cooked in oil containing known quantities of *Argemone* oil produced symptoms of gastro-intestinal irritation, oedema and cardiac involvement closely resembling those found in epidemic dropsy. The active principle present in this oil has a cumulative effect and provided sufficient quantity of the oil is consumed, symptoms appear even though the consumption of the *Argemone* oil or incriminated mustard oil is stopped. The seeds of *Argemone mexicana* resemble superficially mustard seeds. Lal (1941) and his associates have continued their investigations upon this subject and have described a method for isolating a substance which will indicate the amount of Argemone Oil present in Mustard Oil. They believe that the toxicity of the oil corresponds with its content of this substance. They obtained this substance in crystalline form and gave it the empirical formula of $C_{19}H_{15}O_4N$. They have also demonstrated that it has a poisonous effect when added to the basic diet of rats. The oil after removal of the crystalline free base on exposure to light, becomes biologically inactive but administration of the white crystal substance restores the toxicity. Control rats fed on pure mustard oil showed no poisonous effect. They have performed three feeding experiments with a small number of volunteers. In these experiments the control group of one, they state, proves the part taken by Argemone oil in causing epidemic dropsy but the actual toxic principle has not yet been determined since fractions of the oil have not proved toxic.

The symptoms of epidemic dropsy and the pathological changes observed have been discussed fully by Shattuck in Chapter XXX.

The differentiation of this form of epidemic dropsy from the oedema noted in Central Europe and Egypt during the World War may be difficult, the latter apparently being a deficiency disease. In cases in which there is a deficiency of the albumin contained in the blood in epidemic dropsy, egg and milk albumin given in large quantities are recommended for treatment. Thyroid extract has also been recommended and tincture of ephedra, 20–30 minims, with calcium lactate, 10 grains, t.i.d., has also been employed.

Miscellaneous Sources of Plant Poisoning.—In addition to the diseases described, numerous other instances of poisoning by plants are known, some accidental in origin, and some intentional. Steyn (1941) has recorded a number of the important plants that have caused poisoning in South Africa. Chestnut (1898) listed only about 30 species of plants associated with accidental poisoning in man, poisoning with them generally resulting from confusing poisonous plants and harmless ones, as mistaking water hemlock for edible roots. However, Muenscher (1939) lists 400 species of poisonous plants in the United States which have caused poisoning either in man or animals. The families that contain the largest number of poisonous species are the Liliaceae, Ranunculaceae, Leguminosae, Euphorbiaceae, Umbelliferae, Solanaceae and Compositae. Prussic acid occurs in many valuable foods, and, if not removed, may produce serious results and even death. Oxalic acid likewise is contained in variable quantity in many edible plants, as sour grass and rhubarb, and may cause poisoning if ingested in sufficient quantity. The linseed plant, *Linum usitatissimum*, also contains a cyanogenetic glucoside which occurs very early in the development of the plant and persists in the seeds.*

Mandioca Poisoning.—The roots of the plants *Manihot aipi* (sweet cassava) and *Manihot utilissima* (bitter cassava) constitute one of the most important articles of diet of the natives in many parts of Africa or South America and in the West Indies.

* Consumption of unripe persimmons, especially by children in Australia, has at times given rise to more or less serious symptoms due to coagulation of the fruit when it comes into contact with the HCl of the gastric juice and the gumming of pieces together into a fairly firm mass of pulp. They may measure several inches in diameter and often can only be effectually removed by operation.

The roots are generally dried and ground into a powder and used as a flour that forms the basis of cassava cakes. In more civilized areas, starch and tapioca are prepared from the roots. Bitter cassava contains a glucoside which in the presence of water sets free HCN; and, in order to avoid poisoning, the tuber must be scraped, grated, squeezed free of its milky juice, and then thoroughly washed. Then it is often dried in the sun. In cases of poisoning, nausea, vomiting, distention of the abdomen, and impeded respiration occur.

Holland (1938) points out an interesting, though not uncommon, instance of a fruit being both edible and a dangerous poison. This is the ripe fruit of the cultivated tree *Pangium edule* Reinw, which is quite wholesome while the unripe fruit produces illness, or even death. The kernel may be eaten after steeping and baking.

The fruit of the wild tree, at all stages, and the kernel are poisonous and the scraped kernel of the wild fruit, which is sweet like scraped coconut, can be added to food, when its presence cannot be detected. Lethal doses have thus been placed in food, and it has been widely used for homicidal purposes. The chief use of the nut in some villages has been in stealing fowls. The scraped kernels are thrown to fowls and these die quickly after eating them. However, the crop is then removed and the fowl may be eaten. Chemical examinations have shown that the kernels contain hydrocyanic acid in high concentration, probably in combination, as in the case of the glucoside amygdalin.

Various species of *Jatropha* (physic nuts) are found in India and the West Indies, and symptoms of severe gastro-intestinal irritation, more or less like that of croton oil, result from eating the seeds. Similar cases of poisoning have been reported by Raymond from Tanganyika as due to the ingestion of the nuts of the coral plant.

The nuts of the species *Jatropha multifida* taste much like sweet almonds. The leaves of *Jatropha urens* in the West Indies have irritating hairs which may cause swelling of the lips, nausea and prostration. Another species found in the United States from Virginia to Texas, *J. stimulosa* (spurge nettle), produces similar symptoms. Fainting occurs in severe cases.

The manchineel tree (*Hippomane mancinella*, of the order *Euphorbiaciae*) has long been a source of poisoning in the West Indies, northern South and Central America, and Florida. It is a handsome tree, averaging 30–50 ft. in height and a circumference which may reach 5–10 ft. Two varieties are recognized; one with holly-like leaves and the other with laurel-like leaves. The former, is more common. Both are equally poisonous and produce fruit resembling crab-apples, which have sometimes been eaten with fatal results, especially by those unable to obtain other food. However, the taste is pungent and, to some, disagreeable. The latex contains a greenish resin which is the active toxic principle. There is a legend that it is dangerous to sleep under the shade of the tree, as death may result, and it is also said that smoke from the burning wood produces severe inflammation about the eyes. Rain drops falling on the skin of a person sheltering beneath it may cause irritation. All parts of the tree appear to be toxic.

People who are hypersensitive who pick the fruit may suffer from a skin irritation consisting of at first an erythema and later the formation of vesicles and bullae. Con-

junctivitis and inflammatory changes in the other mucous membranes result if the part is touched with the fingers on which the latex is present. If the fruit is eaten, swelling of the lips and blisters and erosions of the buccal mucosa may occur. Nausea, vomiting, and difficulty in swallowing may be present, sometimes liquid stools with blood, and more rarely manifestations of profound collapse occur.

Earle (1938) says the wood shows a handsome grain and polishes well, but local carpenters will not often use it because its sawdust causes cough, rhinitis, laryngitis, conjunctivitis, and lachrymation.

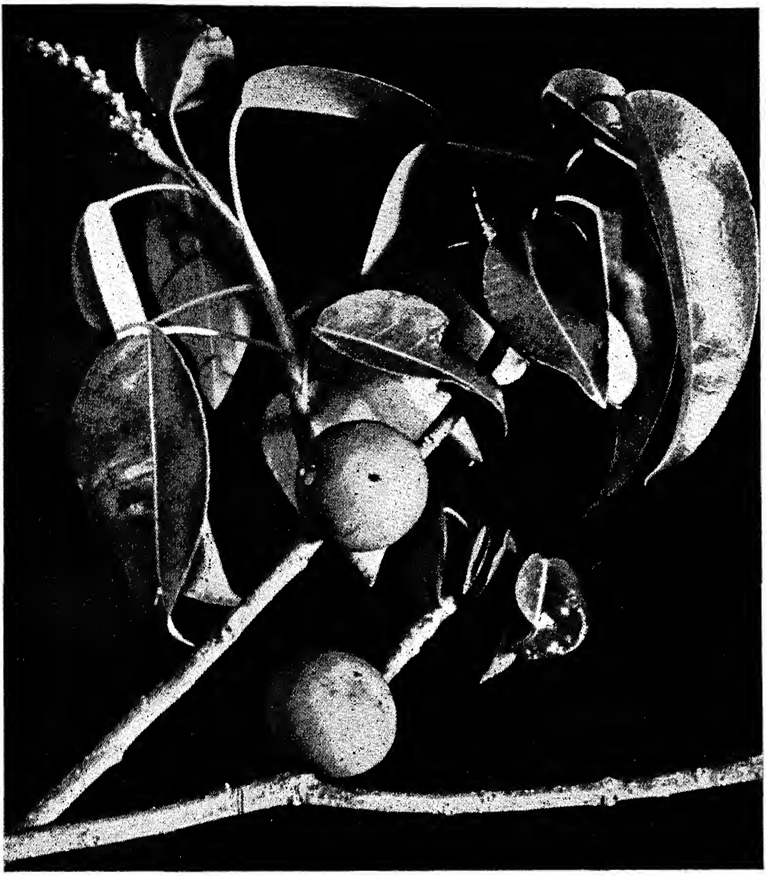

FIG. 269.—*Hippomane manchinella.* Fruit and inflorescence. (Photograph of K. V. Earle, Courtesy Trans. Roy. Soc. Trop. Med. & Hyg.)

Treatment is largely symptomatic. It is recommended that the manchineel juices present on the skin should be immediately washed off with salt water. If the fruit has been eaten, an emetic should be given.

The latex of the plant has sometimes been employed by the natives as a liniment and the dried fruits have been used as a diuretic. The seeds contain a purgative oil.

Plants Especially Used for Criminal Poisoning.—The root of *Gloriosa superba,* a plant widely distributed in tropical Asia and Africa, has been used to produce poisoning. It is sometimes called wild aconite, and the physiological effects, due to the active principle "superbine," are similar to those of aconite poisoning—tingling and numbness

of the lips and pharynx, nausea, vomiting, abdominal pains, cardiac depression and collapse symptoms. Consciousness is retained until the late stages, when convulsions may appear.

Various plants belonging to the order Solanaceae are used in many parts of the tropical world and by criminals in temperate climates to produce unconsciousness. Chopra has reported fatal cases of poisoning from *Jatropha* in India, in which the symptoms were dryness of the mouth and throat, dilatation of the pupils and delirium.

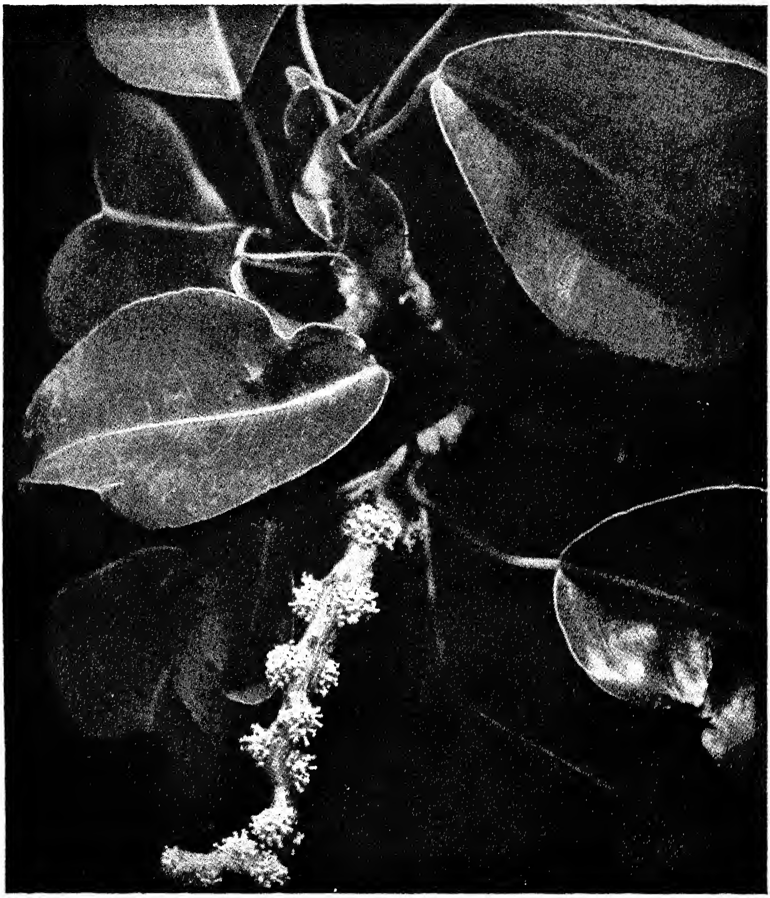

FIG. 270.—*Hippomane manchinella*. Inflorescence. (Courtesy Roy. Soc. Trop. Med. & Hyg.)

The seeds of *Datura fastuosa* are used by the Thugs in India to produce unconsciousness, and various other plants whose alkaloids have a similar action to belladonna are used by the natives of many parts of the tropical world. The seeds of *Datura* have only a slight taste and are consequently easily introduced into food. *D. sanguinea* has been employed in Peru and Colombia and *D. ferox* and *D. arborea* in Brazil. The characteristic seeds are sometimes found in the faeces, or in fatal cases in the intestine.

The dried leaves of *Hyoscyamus niger*, or henbane, is the basis of some of the "knock out" drops used by the underworld. In poisoning from these plants there is a flushed face, widely dilated pupils, with the eyes bright and shining. The throat is very dry. There is marked disturbance of vision. At first the victim is very talkative and soon

becomes violent, but later on drowsiness sets in followed by coma. The yellow oleander, *Cerbera thevetia*, is a very poisonous plant found in India. The poisonous principles are glucosides, nerioside and oleandroside, and are found in the milky latex. Similar substances, urechitin and urechitoxin from *Urechites suberecta*, possess a cumulative action and sudden death may occur before suspicion of poisoning is aroused.

The juice of a species of *Asclepias* (of the Milkweed family) has been used in India as an infanticide. It produces symptoms of vomiting, salivation, and cramps and final collapse. The roots of various species of *Aconitum* already referred to have been used for the same purpose, death often taking place in from 3 to 4 hours.

In New Guinea, Holland (1938) reports that the eating of the roots of wild species of Derris is the commonest form of suicide among the natives. The root is known under the name of "bun" and it has only been identified as Derris root since the plant has become of value as an insecticide. The conditions he found at autopsy are indicative of acute congestive heart failure. The poisonous substance of the species *Derris eliptica* is rotenone. Other toxic resins are also present, as derride. As an antidote, the natives use the sap expressed from the roots of the banana, which is mucilaginous and acts as an emetic.

Common native poisons employed in Brazil are prepared from *Paullinia pinnata*, which contains an alkaloid (timboin) and from the fruit of *Thevetia ahonai*, which contains the poison thevetosin. Both of these cause vomiting and acute respiratory failure. In the Dutch East Indies, the common poison is extracted from the roots of species of *Milletia*. Following its ingestion, debilitation, headache, diarrhoea and collapse usually occur, followed by death.

Jengkol Poisoning.—DeLangen has reported especially the occurrence in the Dutch East Indies of poisoning from eating the pod fruits or beans of *Pithecolobium geminum*, one of the species of the Mimosaceae. The fruit is eaten with great avidity by the natives, although it has a foul odor. It is crushed and roasted before use. The beans are sometimes put through a preliminary appetizing process, which serves to increase their toxicity.

They are first buried in the ground for about 10 days. When they begin to sprout, they are ready for use and are eaten. Jengkol so prepared is called "bèwèh" in Java. The seeds contain aetherial oils and exert a powerful irritating action. If a small amount is taken, there is apparently no other effect than causing the urine to assume a most unpleasant odor, though red blood corpuscles may be found in the sediment. However, if larger amounts are consumed, mild cramps in the loins may follow, as well as spasms in the bladder. The urine then contains some albumin and many red blood cells and leucocytes. The odor of the urine and of the breath makes the diagnosis quite easy. If large amounts are taken, the poisoning is severe and the picture alarming. Intense, colicky pains in the abdomen and loins occur with sometimes vomiting and constipation, coupled with flatulence. Patients are sometimes sent to the hospital with a diagnosis of peritonitis. In some instances, the symptoms resemble strongly those of kidney stone. The urine is highly colored and concentrated, resembling meat juice, containing much albumin and many casts, as well as a large quantity of blood. The urine has the characteristic, penetrating, disgusting odor of jengkol. In some cases, anuria develops and then the diagnosis can be made from the odor of the breath. The most striking constituent of the urine is the sediment of small, sharp, slightly soluble crystals which disappear a short time after the urine has been passed and kept in the laboratory. DeLangen believes that these crystals give rise to the kidney symptoms in a purely mechanical way. Van Veen and Hijman have succeeded in extracting this same crystalline substance from the jengkol beans, which they named "djenkolzuur" (jengcolic acid).

As a further product of decomposition, phenyl-acetic acid was formed. DeLangen points out that apparently the glucoside is related to that of mustard oil formed by

enzymic action. It is this substance that gives the urine its penetrating odor. The anuria usually passes off in a day or two, but the urine continues for a long time to show a trace of albumin. DeLangen has not seen fatal cases. Mreyen (1941) reports two fatal cases; in both the kidneys were very hyperaemic.

The jengkol bean has a high vitamin B content and is used as a food in spite of its toxic properties. In some instances, an increase in the excretion of sulphur is found in the urine.

Opium.—The use of opium is common among the inhabitants of India and the Orient, not to refer to the drug addicts of Europe and America. In India, Persia and Africa, opium is almost invariably eaten or taken in pill form and with its use in this way the ill effects are much reduced. The mental, moral and physical deterioration so common in those who smoke opium, as in China, Malaya, and sometimes in Persia, or who use morphine or other alkaloids hypodermically, is not so marked. There is also less tendency to increase the dose. Every medical man should read DeQuincey's "Confessions of an English Opium Eater" to appreciate the slight effect this habit had on the author for the first few years of his addiction. He took the drug as did the native of India. In the Far East, native mothers and wet nurses sometimes smear the nipples of the breast with the drug and it has been a not uncommon custom for the native nurses, or *ayahs*, to soothe babies to sleep by dipping the finger in opium and giving it to the baby to suck. Such treatment is obviously highly deleterious to the child. The minutely contracted pupils may suggest to the practitioner this form of intoxication in obscure cases of illness.

Erythroxolon Cocoa.—Cocaine has been especially used in India and in parts of South America as a stimulant or intoxicant. In India the drug is chewed with betel nut and slaked lime (*chunam*). In the uplands of Peru and Bolivia the leaves, which are first dried in the sun, are also chewed with lime. The natives have the custom of making a ball of the leaves, which they carry most of the day between the mucous membranes of the gums and cheek. The drug produces at first a loss of sensation in the tongue and lips, followed by dryness of the mouth and fauces, the pulse becomes accelerated, and a period of hilarity or exaltation due to over-stimulation of the nervous system occurs. From the chronic use of the drug, however, the taste is soon abolished through the anaesthesia of the nerve terminals. Pernicious symptoms soon develop. The individual becomes emaciated and cachectic. There is often insomnia and digestive disturbances. The appetite is lost, and the individual soon becomes undernourished and vitamin deficiency disease is likely to ensue. A large percentage of the native inhabitants have become addicted to this habit in the mountainous regions, especially of Peru and Bolivia.

Dhobie Mark Dermatitis.—Livingood, Rogers and Fitz-Hugh (1943) have described 52 cases of "dhobie mark dermatitis" resulting among American soldiers serving in India due to articles of clothing worn by them that had been marked with the juice of the marking nut. They were informed that the marking fluid used by the "dhobies" throughout India is obtained from the nut of the *ral* or *bela gutti* tree. The exact localization of the circumscribed patches of dermatitis on that part of the skin in contact with the dhobie mark and the course of the lesions, made it quite obvious that this represented a contact dermatitis induced by the marking fluid which the native dhobies or washermen used in making their characteristic laundry marks. A large series of patch tests was made, not only to prove the causation but also to establish constant factors so that the true incidence of sensitivity could be determined. Of previously affected persons, 80% were positive to patch tests. The first symptoms were, localized pruritis at the site of contact with the mark during 8–24 hours. This was followed by localized lesions varying in severity from moderate erythema and oedema to definite vesiculitis, oozing and crusting. One or

more of the following sites were always involved; nape of the neck and upper back, waist line (anterior, posterior or on one side), sides of the ankles, dorsal surfaces and sides of feet and lower one-third of the legs. In every case the sites of the lesions corresponded exactly with one or more of the dhobie marks on their recently laundered clothes worn by the individual. Recurrence of lesions was noted promptly if marked clothes were again worn.

As their article implies, this form of dermatitis should not be confused with *Tinea cruris* infection which is described on page 1168 of this book.

Dhobie itch has been a well recognized form of trichophyton infection among white soldiers and civilians in the Philippine Islands since the early days of American occupation in 1899. It is not the custom of Philippine washermen to mark clothing in this manner. The trichophyton fungus may almost invariably be found in scrapings of the skin from the lesions. (See p. 1170.) This form of dhobie itch is an entirely different affection from that referred to by Livingood, Rogers and Fitz-Hugh.

Waud and Fein (1943) have also referred to this form of dermatitis in our troops in India caused by the ink from the bichi nut used in marking clothing. They produced the lesions experimentally by placing some of the juice of the nut upon the skin. In 12–24 hours a reddened area appeared around the patch. In the severe reactors the patch became swollen, the macular area changed rapidly to a papular and then vesicular type of lesion. The itching was intense and the heads of the vesicles were soon removed by scratching. The treatment is primarily by removal of the cause.

Goldsmith (1943) has reported dermatitis affecting 16 persons (employees of one of the large government departments in Washington) due to handling mail contaminated with the juice of the "bhilawanol or the Indian marking nut." A bottle in a sealed mail pouch, shipped from India by air, had become partially opened and its contents (thick black oil) had contaminated various pieces of mail. The contaminating substance was labeled "bhilawanol oil." Three workers who were unpacking the pouch wiped the oil off the mail as well as they could. It was then distributed by a force of carriers and clerks, numbering approximately 50. By evening a number of workers complained of itching and burning of their hands, arms and face. Within 24 hours a vesicular eruption appeared on the exposed parts. Some of the workers did not touch the mail until as long as 5 days after it was unpacked but these also developed an eruption 24–28 hours after contact. Eventually 16 of approximately 50 exposed persons developed dermatitis of varying degrees of severity. The appearance was similar to that of typical dermatitis venenata from *Rhus toxicodendron*. The oil is obtained from the juice of the marketing nut, the *Semecarpus anacardium*. It is a member of the same family, Anacardiaciae, as the severe irritant Rhus plants of Mangifera, the cashew nut and the agent causing dermatitis in Japanese lacquer and the Mango. (See page 1209.)

Merrill (1944), (an eminent authority) points out that it is evident that as the war progresses there will be other cases of dermatitis observed in the active and potentially active areas caused by species of the *Anarcardiacae* which have such a world wide distribution and he lists a number of the more important species which are liable to give rise to disturbing dermatitis in tropical countries. He adds that on the whole he suspects that it will be only on rare occasions that cases of anarcardiaceous dermatitis will be noticed, and if such cases do show up then one should apply the same treatment that one would use for *Rhus* dermatitis at home.

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SECTION VII

ANIMAL PARASITES, INCLUDING HELMINTHS, INJURIOUS ARTHROPODS, POISONOUS FISH, SNAKES, AND COELENTERATES

Chapter XLIII

COMMON COSMOPOLITAN HELMINTHIC INFECTIONS

General Considerations

Surveys in various parts of the tropical world often show more than 90 per cent of the children and almost as high a proportion of adults to be infected with helminths. Of the cosmopolitan round worms, *Ascaris* and *Trichuris* are the most common, and of the tape-worms, *Hymenolepis nana*. These 3 helminths do not require an intermediate host in their life history, so that the unhygienic ways of living of the most primitive peoples give opportunity for almost universal infection.

The morphology of any one of these parasites and the appearance of the ova, as well as the treatment of the infection, are the same, whether it is encountered in tropical or in temperate climates. However, all of them are found more frequently and in far heavier infections in the former than in Europe or America.

With such round worms as *Trichinella spiralis*, or with tapeworms *Taenia saginata*, *T. solium*, and *Diphyllobothrium laium*, secondary hosts are involved in the life cycle. Even if introduced into new territory, such infections fail to spread if the custom of eating raw or insufficiently cooked pork, beef, or certain kinds of fish does not exist among the natives. The trematode parasites of man all require two or more hosts in their life history.

In many parts of the tropics, it is usual for the patients in the native clinic to harbor the round worm, *Ascaris*, the whip worm, *Trichuris*, the hook worm, *Ancylostoma* or *Necator*, or at times all three. However, it is of course, advisable to have accurate laboratory data as to the presence of the ova of intestinal parasites, more particularly as to *Ascaris*, so that in getting a history we may not be led astray by complaints of intestinal disturbances. Stiles has stressed the fact that the beef tape-

worm may cause symptoms very varied in character, and the same might be said of the ubiquitous round worm.

CLASSIFICATION OF THE NEMATHELMINTHES (ROUND WORMS)

Class Nematoda

Superfamily	Family	Genus	Species
Rhabdiasoidea	Strongyloididae	Strongyloides	S. stercoralis
Trichuroidea	Trichuridae	Trichuris	T. trichiura
	Trichinellidae	Trichinella	T. spiralis
Strongyloidea	Ancylostomidae	Ancylostoma	A. duodenale
			A. braziliense
		Necator	N. americanus
	Strongylidae	Ternidens	T. deminutus
		Oesophagostomum	O. apiostomum
			O. thomasi
		Syngamus	S. laryngens
	Trichostrongylidae	Trichostrongylus	T. colubriformis
		Haemonchus	H. contortus
	Metastrongylidae	Metastrongylus	M. apri
Dioctophymoidea	Dioctophymidae	Dioctophyme	D. renale
Oxyuroidea	Oxyuridae	Enterobius	E. vermicularis
Ascaroidea	Ascaridae	Ascaris	A. lumbricoides
		Toxascaris	T. leonina
		Toxocara	T. canis
Spiruroidea	Spiruridae	Physaloptera	P. caucasica
		Gongylonema	G. pulchrum
	Gnathostomatidae	Gnathostoma	G. spinigerum
		Thelazia	T. callipaeda
Filarioidea	Filariidae	Loa	L. loa
		Wuchereria	W. bancrofti
		Filaria	F. malayi
		Mansonella	M. ozzardi
		Acanthocheilonema	A. perstans
		Onchocerca	O. volvulus
	Dracunculidae	Dracunculus	D. medinensis
Acanthocephala (Class)	Gigantorhynchidae	Macracanthorhynchus	M. hirudinaceus
	Moniliformidae	Moniliformis	M. moniliformis
Annelida (Phylum) Hirudinea (Class)	Hirudinidae	Hirudo	H. medicinalis
		Limnatis	L. nilotica
	Haemadipsidae	Haemadipsa	H. zeylanica

The subphylum Nemathelminthes is divided into two classes: the Nematoda which possess a gut but are without a proboscis and the Acanthocephala in which the gut is absent but proboscis present. The former includes the subclasses Eunematoda and Gordiacea of which the latter are accidentally parasitic in man. The Eunematoda contains normally free-living forms (order Vagantia of some authors) which are occasionally introduced accidentally into man and the more important parasitic forms (order Parasita of some authors). Eight superfamilies of the parasitic forms are included in the Key from Yorke and Maplestone, but several of the groups here classed as families are regarded as superfamilies by some authorities.

Note.—The Annelida are grouped with the round worm table for convenience only and not to show taxonomic relationship. The Acanthocephala are not closely related to the nematodes, and their taxonomic position is still in doubt.

Classification of the Nematoda (Round Worms)

The nematodes are cylindrical, non-segmented parasites, usually tapering at both ends. They are white, red or yellow or brownish in color and sometimes semi-transparent.

All nematodes are covered with a cuticle varying in thickness and frequently ringed. Characteristically the cuticle is moulted four times during development. The cuticle is formed by the underlying ectoderm which is as a rule markedly thickened internally so as to form four ridges which divide the body into quadrants. Within the ectoderm is the body cavity, a space containing clear fluid in which the reproductive organs lie. The excretory system usually consists of two tubes which discharge near the head.

While the alimentary canal is more or less tube-like in appearance it shows near the mouth a distinct oesophagus. This may have a scanty musculature and lie apposed to a single row of large secretory cells (Trichuroidea); it may be muscular without a globular bulb (Strongyloidea) or muscular with a posterior bulb (Oxyuroidea). In Filarioidea and Spiruroidea the oesophagus may be divided tandem. There is a nerve ring around the oesophagus.

The testis and ovary are generally tube-like. The sexes are, as a rule, separate. The male can usually be recognized by its smaller size, its curved or curled posterior end, at times exhibiting an umbrella-like expansion—the copulatory bursa. The spicules, chitinous copulatory structures, may be observed drawn up in the worm or projected out of the cloaca. The genital opening of the female is ventral and may vary in position from close to the mouth to near the tail. That of the male is close to the anus, and both open into a common cloaca which opens in the ventral line as the cloacal aperture. Certain papillae in the region of the anus are valuable in differentiation of species.

Many nematodes develop in damp earth from the eggs as rhabditiform larvae. Very few nematodes are viviparous (*Wuchereria*, *Trichinella*), most of them being oviparous (*Ascaris*).

The parasitic Eunematoda are divided into at least eight superfamilies.

Key to Superfamilies
(Modified from Yorke and Maplestone)

1. Heterogenetic, parasitic form parthenogenetic....................Rhabdiasoidea
   Not heterogenetic, parasitic forms sexually differentiated.................... 2
2. Oesophagus consisting of a narrow tube with reduced musculature in association with a row of single oesophageal cells, the stichocyte...............Trichuroidea
   Oesophagus not of this type.................................... 3
3. Males with a bursa copulatrix.................................... 4
   Males without a bursa copulatrix.................................... 5
4. Bursa copulatrix cuticular and supported by rays.................Strongyloidea
   Bursa copulatrix muscular and not supported by rays..........Dioctophymoidea
5. Oesophagus dilated posteriorly into a bulb usually containing a denticular apparatus and frequently separated from the rest of the oesophagus by a constriction.... Oxyuroidea
   Oesophagus not dilated posteriorly into a bulb.............................. 6
6. Head with three large lobes or lips: relatively stout worms.............Ascaroidea
   Head without three large lobes or lips but with two lateral lips, or 4 or 6 small lips, or lips absent; relatively slender filiform worms.............................. 7
7. Usually with two lateral lips, chitinous buccal cavity or vestibule usually present, vulva usually in the middle of the body or posterior to it; parasites of alimentary canal, respiratory system, or orbital, nasal or oral cavities.............Spiruroidea
   Usually without lips, buccal cavity or vestibule absent or rudimentary, vulva almost invariably in the oesophageal region; parasites of the circulatory or lymphatic system, or muscular, or connective tissue, or of serous cavities..........Filarioidea

The family Anguillulidae (normally free-living nematodes occurring only accidentally in man) contains the genera *Rhabditis* and *Anguillula*. Several species of *Rhabditis* have been reported from man. *Anguillula aceti*, the vinegar eel, has been reported from the genitourinary tract several times. Such cases can be explained by the prior contamination of the urine bottle, or by the use on the part of the patient of a vinegar vaginal douche.

SUPERFAMILY I—ASCAROIDEA

The parasites of this family have a mouth commonly provided with 3 prominent lips supplied with papillae, 1 dorsal and 2 ventral, but lacking a buccal capsule Fig. 271. The oesophagus is muscular and usually without posterior bulb. Males without a bursa copulatrix and usually without caudal alae.

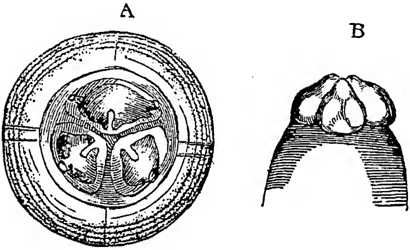


FIG. 271.—Anterior extremity of *Ascaris lymbricoides;* A, seen from front; B, seen from dorsal surface. (Tyson after Railliet.)

Genus Ascaris Linnaeus, 1758.—This genus includes those species of ascarids in which the lips have dentigerous ridges, but in which cervical alae are absent. They are relatively stout worms.

The male is smaller than the female and has a conical tail, without caudal alae. In front of, and behind the cloaca, there are numerous papillae. The spicules are equal in size and have no lateral wings.

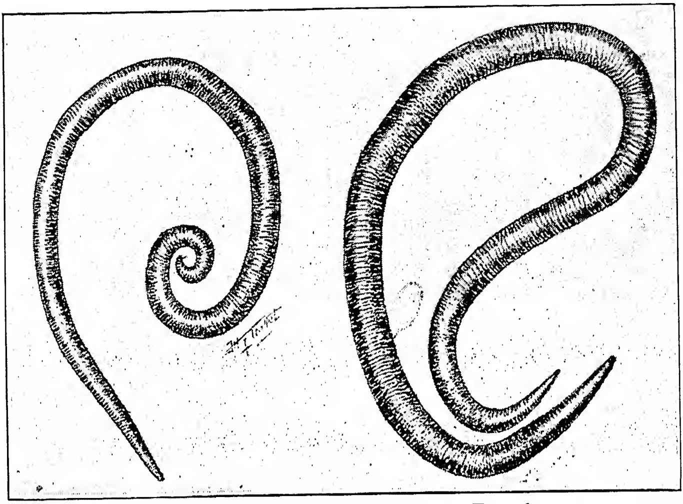
In the female the vulva is double and situated in front of the middle of the body. The eggs are characteristic in that they are brownish in color and have a thick, smooth shell, surrounded by a corrugated or mammillated albuminous coat, and in that they contain a large unsegmented ovum when passed in faeces.

Type-species: *Ascaris lumbricoides* Linnaeus, 1758.

Ascariasis caused by infection with *Ascaris lumbricoides*, which is probably the most common helminthic infection of man, especially of children. A species morphologically identical has been encountered in pigs and in the gorilla. It occurs throughout the world, in temperate as well as tropical regions, and has been reported from the arctic regions. The most severe injections are encountered usually in tropical countries where in the warm, moist climate personal hygiene and environmental conditions combine to favor embryonation of the ova in polluted soil.

Morphology.—The parasite is large (from 25–40 cm. in length) and in shape and size somewhat resembles the common earth worm, being yellowish white and a light brown in color. The female genital system is double. The worms are cylindrical, tapering to a blunt point at each end. The body is transversely striated. The females are usually 20–36 cm. long and 4–5 mm. in diameter. The males are slightly more slender and shorter, and from 15–30 cm. long. The mouth is provided with 3 papillae-like lips with finely denticulated margins, marked off from the rest of the body by a sharp constriction. The cloaca is near the posterior tip, and from it in the male projects two large lance-like copulatory spicules. The posterior extremity of the male, unlike the female, is curved ventrally, and has 7 pairs of post-anal papillae. The uterus consists of long, whitish convoluted thread-like tubes terminating in oviducts which lead to the vulval orifice on the ventral surface at the junction of the anterior and middle thirds of the body. It has been estimated that the genital ducts of the female *Ascaris* contain about 27,000,000 ova.

After fecundation, the females discharge enormous numbers of ova, estimated at about 200,000 each daily. They are eliptical, 40–50μ by 60–75μ. They are provided with a thick, smooth, translucent inner shell and a rough, mammilated outer coat which is sometimes lost. The contents are granular, not segmented, and usually show a clear crescentic area at each pole (Fig. 274). Eggs which are deposited unfertilized are markedly abnormal in their appearance, often longer, irregular in shape, and sometimes grotesquely misshapen, with structureless, granular contents, so that they may be mistaken for vegetable cells. Their occurrence may indicate that the host harbors only female worms. Occasionally in human faeces the albuminous coat of the fertilized egg disappears and it is then somewhat difficult to recognize. The presence of the large ovum entirely filling the egg is, however, sufficiently characteristic to identify it. A small spore, or seed, is not infrequently found in human faeces. It superficially resembles an *Ascaris* egg. It is, however, considerably smaller, 10–20μ. It does not contain an ovum.



Male — Female

FIG. 272.—*Ascaris lumbricoides*. (Male and female.) Natural size. (After Brumpt.)

Life History.—There is no intermediate host. The ova in fresh faeces are unsegmented and non-infective. In the presence of warmth (but not at body temperature) a little moisture and oxygen, segmentation occurs outside the body, and development of the embryo is completed after an interval of from 10 to 40 days or more (rarely less than 30) depending upon the temperature (optimum 30°C.). Normally the larva remains within the shell until ingested. However, hatching can be induced by first desiccating and then moistening the ova, and the larvae may live for several weeks in moist earth (Kondo). The ova are very resistant to the usual chemical disinfectants, to cold (down to −15°C.) and to desiccation at moderate temperatures, but are usually killed by desiccation in hot weather. Eggs have remained viable 4 years when stored moist at ice box temperatures, and 2 years when dried.

Infection.—It is generally believed that infection normally occurs by swallowing "embryonated" ova. Infection is heavy in regions in which soil pollution is common, or in which human faeces are used as fertilizer. Ova may be conveyed to the mouth by dirty fingers (especially in children), or by contaminated water, green vegetables, or other food, and possibly by inhalation. Scott (1939) has shown that in Egypt the infection is

transmitted primarily by direct hand to mouth transfer of eggs which have developed on the moist floors of the house. The larvae (0.24 mm. long) are liberated in the contents of the small intestine.

Stewart (1916), Ransom and Foster (1917), and Ransom and Cram, (1921) and, independently, the investigations of Fülleborn (1920–26) demonstrated that these larvae penetrate the wall of the small intestine, reach the mesenteric lymphatics or mesenteric venules, and are carried through the right heart to the lungs. Here, after a sojourn of several days, they usually break through the pulmonary capillaries into the air sacs and are carried up the bronchioles, bronchi and trachea to the epiglottis, are then swallowed and pass down to the small intestine, where they develop into adult males and females.

In individuals exposed to heavy inoculations with infective-stage eggs, some of the larvae may pass through the pulmonary capillaries into the left heart and systemic circulation and may be filtered out in various organs and tissues of the body, as the lymph nodes, the thyroid, thymus, spleen, the brain and spinal cord, where they may set up unusual clinical manifestations; they may accumulate in numbers in the kidneys and be passed in the urine; or they may even pass the placental filter of pregnant mothers and reach the foetus. During the sojourn in the lungs, the larvae moult twice (once after 5 or 6 days, the second time after the 10th day), reach a length of 1 to 2.1 mm. (average, 1.5 mm.) and acquire a resistance to gastric juice by the time they reach the stomach. While in the lung, if the infection is heavy, the parasites give rise to bronchitis with considerable bleeding, or even to an "ascaris pneumonia" accompanied by fever and eosinophilia. They may be demonstrated in the sputum. This passage through the lungs seems to be essential for the development of the worm.

On reaching the intestine, the larvae (2.0 to 3.0 mm. long) develop into adult forms after a period of 8 to 10 weeks. The life span of the adults has been estimated at about a year.

This cycle has been demonstrated by feeding mature *A. lumbricoides* ova to rats, guinea pigs and hogs. In these animals the ova hatch, and the larvae migrate to the liver, lungs and back to the intestine (although in such unsuitable hosts development usually does not go on to the production of mature adults). The same appears to be true in man. Koino, e.g., swallowed 2000 mature *Ascaris* ova and developed pronounced symptoms of lung involvement with bloody sputum containing larvae. Fifty days later, following an anthelmintic, 667 worms were recovered. Yoshida swallowed larvae taken from the lung of a guinea pig and ten weeks later ova appeared in his faeces. In such feeding experiments, however, the proportion of larvae which succeed in establishing themselves in the intestine is usually very small, and occasionally none have done so. This fact and other indirect epidemiological evidence led Lane to suggest that infection may occur by *inhalation of desiccated ova in dust*. The ova may hatch on the moist mucous membranes of the upper air passages and the larvae penetrate directly into the blood stream without being swallowed. There is some evidence that under experimental conditions hatched larvae may penetrate the skin, but this is not known to occur under natural conditions.

The round worm of the pig, *A. suilla*, is morphologically identical with *A. lumbricoides*, but it has been suggested that it is biologically distinct. Feeding experiments of the Koino brothers suggested that neither parasite will develop to maturity as a rule except in the homologous host. Lane (Critical review, 1934), however, doubts the validity of this evidence and believes the question is still open. Blacklock (1938) points out that as experimental attempts to infect man with the larvae derived from the pig *Ascaris* have failed, the species found in the pig may be physiologically distinct

Ransom showed that a serious lung disease (thumps) of little pigs is caused by *Ascaris* larvae passing through the lungs.

Toxocara cati (*Belascaris cati*) and *Toxocara canis* (*Toxascaris canis*), the common ascarids of the cat and dog respectively, have sometimes been reported for man; 9 recorded cases for the former and 1 of the latter. They are much smaller than *A. lumbricoides*, averaging about 3 inches in length and are characterized by wing-like projections from the anterior end by reason of which they are called the arrow-headed ascarids. The eggs are thick shelled and somewhat similar to those of *A. lumbricoides*. *Toxascaris leonina*, the type species has been found in Carnivora.

Lagochilascaris Minor, Leiper, 1909.—This ascarid is a normal parasite of the small intestine of the cloudy leopard, *Felis nebulosa*, and has been recovered 5 times from abnormal foci in human cases: from subcutaneous abscesses of the neck near the angle of the jaw, from tonsillar abscesses, and from the orbit in 4 natives of Trinidad, and once from a mastoid abscess of a patient in Dutch Guiana.

According to Faust, the adult male worms measure 9 mm. in length by 0.4 mm. in diameter; the females, 15 mm. by 0.5 mm. in diameter. The worms lack cervical alae, but are provided with a triangular keel along the entire lateral line. The three lips are invested with a thickened raised cuticle, each with a conspicuous verticle cleft, and the entire labial structure is separated from the cervix by an engirdling furrow. There are about 24 pairs of preanal papillae arranged in a single longitudinal row in the ventro-lateral position on each side of the median ventral line, a twinned pair and 4 single pairs of postanal papillae. The vulva is pre-equatorial. The eggs are globose, moderately thick-shelled, superficially pitted, measure about 65 microns in diameter, and resemble those of *Toxocara cati*. Although the life cycle is unknown, it is probably direct, with or without a required lung migration. In the human cases reported, the worms had obviously become lodged in abnormal foci, where they had been able to mature and provoke suppurative processes and abscesses.

Pathogenicity of Ascaris.—In mild infections, the symptoms may be trifling. Disturbances may in some instances be produced by the migrating larvae and others by the adult worm. The migration of the larvae through the walls of the intestine into the liver and lungs gives rise to numerous minute hemorrhages. The diameter of the larvae in passing from the pulmonary capillaries to the terminal air spaces is considerably greater than that of the capillaries themselves, hence more or less trauma and petechial haemorrhage takes place. Small confluent haemorrhages may occur in the alveoli and smaller bronchioles, giving rise to some oedema. In some instances there is a local infiltration of polymorphonuclear and eosinophilic leucocytes about the parasites, and these, with the desquamated epithelium and serous exudate may fill the air spaces and produce consolidation. The respiration may be seriously embarrassed, and in extreme cases complete consolidation of the lobes may occur.

Keller (1932) points out that this condition of ascaris pneumonitis, or ascaris pneumonia, is particularly important in children. Koino (1922) after swallowing many eggs in the infected stage, suffered with a marked rise in temperature and severe pneumonia. In children, there may be an elevation of temperature to 39 or 40°C. 1 to 5 days after exposure to infection, with frequent spasms of coughing, bronchial rales, and signs of lobular involvement. Hemoptysis may occur, with larvae in the blood-tinged sputum. Usually these symptoms subside on the sixth or seventh day, but it is regarded as probable that small children and others who are exposed to very heavy infection may at times succumb to pneumonia, especially when complicated by a secondary bacterial infection. If the larvae reach the general circulation, they may be filtered out and in certain foci both mild or severe symptoms depend on their number and location. Disturbances have been reported from their presence in the

brain, spinal cord, and in the kidneys. In their passage through the liver from the intestine and the lungs, they are not believed to produce appreciable symptoms.

Symptoms Produced by the Adult Worms.—The adult worms frequently live in the upper small intestine, but as they wander about within the body they are found in other sites. As a rule the number present is small, but rarely many hundreds may be present. If numerous, they tend to aggregate in clumps which may be demonstrable in roentgenograms as filling defects, and may cause intestinal obstruction. The worms may migrate up or down the intestinal tract, being passed per anum or vomited when they reach the pharynx. They may penetrate into any accessible passage or space and cause bizarre and sometimes serious local

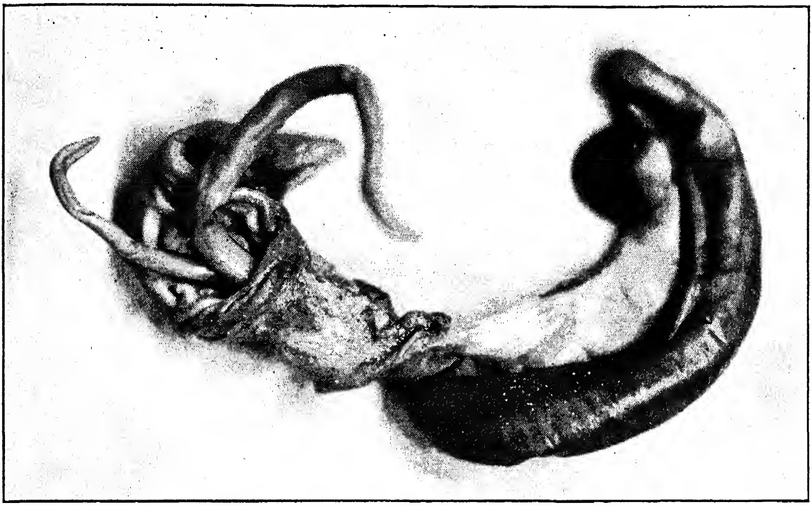


FIG. 273.—*Ascaris* in appendix.

disturbances; e.g., into the appendix, bile ducts, gall bladder, pancreatic duct, nose, sinuses, middle ear and larynx. In some instances they have perforated intestinal ulcers. Guiart, and also Brown (1934) considers it probable that *Ascaris* may suck blood and sometimes cause intestinal ulceration and bacterial infection. Faust (1940) states that at times they may pinch off small masses of the intestinal epithelium. Rajahram (1938) has reported the case of a girl of 6 who died with 5 *Ascaris*-containing abscesses in her liver.

One abscess had opened in the epigastric region, leaving a sinus from which 3 ascarids had escaped while she was under observation in the hospital, when she had emaciation, fever, and an enlarged liver. At autopsy there were still 2 worms in the cavity into which the sinus ran. The dilated and inflamed bile ducts showed other worms and there was one in the duodenum, though santonin during life had not led to the passage of worms. They have also been found in pulmonary abscesses.

Millan (1938) reports a child of 11 months who died of suffocation, the result of several ascarids in the trachea. There were also more found in the stomach and intestine.

Oedema of the glottis may occur, and the writer has seen suffocation result from vomiting a mass of worms in a cholera patient.

Figure 273 illustrates a number of worms obstructing the appendix. Faust also illustrates a case in which the parasites blocked the appendix of a child aged 6 years, with an antimortem diagnosis of "acute abdomen."

Exploratory celiotomy revealed 9 worms in the peritoneal cavity in addition to others which were blocking the appendiceal lumen. The child died of peritonitis.

Chanco (1938) reports a case of a child 3 years of age in which there was a discharge from the umbilicus from time to time since birth. An *Ascaris* presented itself and was removed by forceps, after which the discharge ceased.

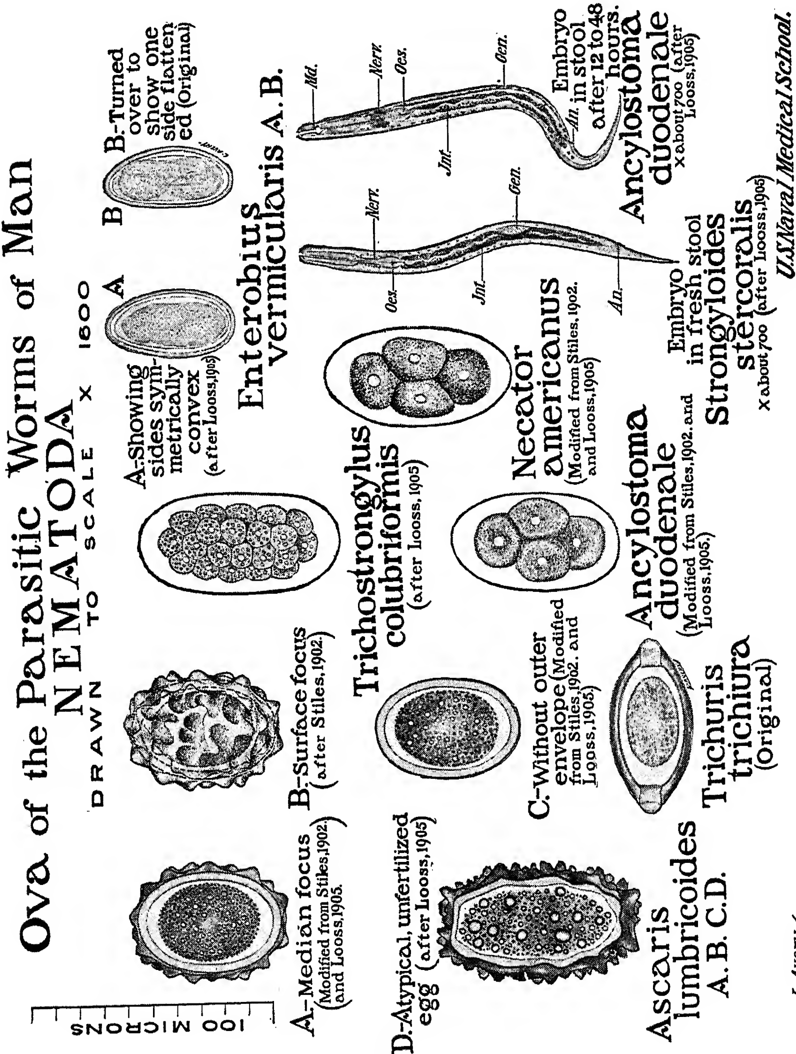


FIG. 274.—Nematode ova.

Girges (1934) has found different extracts of *Ascaris* to contain toxins including anaphylaxins, neurotoxin, haemolysins and endocrinotoxins. In children, *Ascaris* infection sometimes gives rise to pallor of the face, with blue rings under the eyes, and interferes with nutrition. Restlessness, vague abdominal pains and nausea are not uncommon symptoms.

Sang (1938) has demonstrated that *in vitro* watery extracts of *Ascaris* contain a readily diffusible protease which can inhibit the action of pepsin and trypsin by combining with it. This substance is found in different tissues of both the male and female worm, but in variable amounts in different organs. The substance is of the order of a primary albumose. It is only slowly destroyed in acid, rapidly in alkali, and is not digested by trypsin. To this substance he has given the name ascarase.

The experimental data shows that if the worms are at all abundant in the host's intestine the quantity of inhibita produced would play a significant part in decreasing the amount of protein digested by the host. It would appear that in heavily infested animals nutritional symptoms may be due to inability to digest the protein constituents of their diet and that there can be little doubt that this is brought about, at least in part, by the inhibitory action of ascarase.

Laboratory diagnosis depends upon finding the ova in the faeces, or the adults after a vermifuge. It is usually easy, since the typical ova are unmistakable and numerous (about 2000 ova per gram for each female). Ova which have lost the outer shell, or unfertilized ova, may be difficult to identify. Even if there is only a single female worm present, the daily brood of eggs is large enough so that some of them may be seen in the centrifugalized specimen of the faeces.

Nevertheless, Hsu and Chow (1939), in a large series of some 800 autopsies through a number of years, found that *Ascaris* was present in the intestine in 312, or 38 per cent. However, during life stool examinations had been made in 149 and in 44 no ova had been found, so that the stool examination detected only 70.4 per cent of the infected persons. This only emphasizes the care with which the examinations must sometimes be conducted. In 30 of the cases there were only male worms. According to Yokogawa (1932) male worms only, may be present in the bowel in about 3 per cent of the cases. In such instances, the diagnosis may be suggested by the clinical manifestations.

In the early stages of the infection, the diagnosis of pulmonary disturbances caused by the migrating larvae may be difficult. Keller and his associates (1932) believe that repeated migrations of the larvae to the lungs may give rise to an increase in the bronchovascular markings.

The skin test has been suggested for diagnosis. Bachman points out that a positive test does not necessarily imply infection at the time it is obtained. A commercially available *Ascaris* antigen is prepared by the Lederle Laboratories. It is not regarded as of practical value for diagnosis.

Prognosis

The prognosis as a rule is excellent. In cases of acute abdominal symptoms, operation in time may save the patient's life. Cases with pulmonary symptoms may demand careful nursing to insure recovery.

Prevention

Human *Ascaris* infection is primarily acquired by the introduction of the infective stage ova into the digestive tract. The ova are usually derived from human sources, since there is no definite evidence to show that porcine infection plays a part in the epidemiology and etiology of human ascariasis. The infection is usually spread primarily within the household and hence proper sanitary facilities in the house is one of the most effective means of control. While it is present in all age groups, it is especially an infection of small children from 1 to 5 years of age.

Cort and his colleagues have shown that both in the tropics and the southern United States ascariasis is essentially a dooryard and household infection, primarily propagated by the "seeding" of the soil immediately around the house with eggs which are present in the faeces of small children who, in turn, become reinfected from eggs which they pick up on their fingers and introduce into their mouths. The eggs deposited in such localities may remain infective for many months. *Ascaris* prevalence in rural districts where latrines are in use is one of the most sensitive measures of the employment of sanitation. In the southern United States, Cort, Otto and Spindler showed that even if all the people except a few of the youngest children used privies the infection might still be maintained at a high level.

Whenever it is possible, all infected patients should be given prompt treatment to eliminate the parasites. However, reinfection from the contaminated sites will probably occur in many instances. Hence successful results can only be expected through hygienic conditions and the substitution of flush toilets for privies or latrines, and by public health training in schools or by public health nurses in the homes.

In countries where human faeces are used for fertilization, all raw vegetables are apt to be infected. There is no definite evidence that infection may occur by the cutaneous route, but in some countries currents of moist air may pick up the eggs in fine silt and in this way they may be inhaled and reach the pharynx and be swallowed. It has been suggested that such infection has occurred in northern Asia and in Africa. In support of this, Bogojawlenski found *Ascaris* eggs in the nasal mucus of 3.2 per cent of school children examined.

Treatment.—For years the classical remedy for the treatment of *Ascaris* has been santonin, given in doses of 0.1 to 0.2 grams for adults and with children about 0.01 gram for each year of age, followed by a saline purge. However, in the tolerated doses it is very frequently insufficient. If given in efficient doses it is extremely toxic. It may cause visual troubles even in small doses, and give a brownish-yellow color to the urine. In excessive dosage, it may cause vomiting and convulsions.

Its use was largely replaced by oil of chenopodium. This drug is efficient, but it is also very toxic. Smillie reports that in the treatment of over a million people in Brazil with this drug that there were 22 deaths. Four persons to whom he administered the drug died with convulsions. Faust believes that oil of chenopodium should never be employed in the treatment of ascariasis alone, but that it may be employed in conjunction

with the treatment of an accompanying hookworm infection in the following way.

(1) A preliminary dose of sodium sulphate should be given the night before. (2) In the morning, on an empty stomach, the patient remaining in bed, a combined anthelmintic mixture totaling 3 cc. (3 minims per year of age for children), consisting of tetrachlorethylene (2.7 cc.) and oil of chenopodium (0.3 cc.), is administered at one time in capsules or in a teaspoon with sugar. (3) Two hours later a follow-up saline purgation is carried out to remove the moribund worms and to prevent absorption of the drugs by the intestinal wall. (4) The patient remains in bed and takes no food until a copious bowel passage has been obtained. Under proper care, this combined therapeutic procedure has been regarded as both safe and efficient and has no contraindications. It may be repeated after 5 days. However, the great undesirability of oil of chenopodium is that its toxic dose is very close to the therapeutic dose.

Hexylresorcinol has also been advocated. Momma (1938) has reported 90 cases treated in Japan with this drug. The cures varied from 30 to 65 per cent in the different groups. Over 50 per cent showed some unfavorable symptoms from the action of the larger doses of the drug, and in some cases in which larger doses were given, the percentage cured was reported to be lower.

Smillie (1939), while admitting that an ideal 'helminthic has not yet been discovered, recommends hexylresorcinol, which he has found will remove 90 per cent of *Ascaris* in a single administration without danger to the host. A single gram dose for adults is recommended early in the morning or on empty stomach, followed in an hour by a saline purge with no food taken until noon. For children, the dose is 0.6–0.8 gm.

Faust (1940) believes that a most efficient treatment, with a maximum of safety and a minimum inconvenience both to the physician and to the patient, is to be found in caprokol (hexylresorcinol crystoids). The drug is not only most efficient, but is less toxic. It is issued in 0.2 gm. hard gelatin capsules and is administered in the morning on an empty stomach without need of a preliminary purge (1 gm. for adults, 0.6 gm. for children under school age, 0.8 gm. for those between 6 and 10 years of age). Two hours later a saline purge is administered to remove the dead and dying worms. Food is proscribed for 5 hours. The only additional necessary precaution is to require the capsules to be swallowed without being cracked open or chewed up, to prevent chemical irritation of the buccal mucosa by the free drug. In the average group of individuals this therapeutic removes up to 95 per cent of all *Ascaris* worms and produces up to 90 per cent cures. If necessary, it may be safely repeated within 3 days.

None of the anthelmintics used in the evacuation of *Ascaris* from the intestinal tract is effective in killing the larvae during their migration period through the body.

OXYURIASIS OR ENTEROBIASIS

Due to *Oxyuris* or *Enterobius vermicularis* of the superfamily *Oxyuroidea*.

Worms with three-lipped mouths. Lips simple or indistinct. Oesophagus shows definite posterior bulb, usually containing a denticular apparatus. Example, pinworms of family Oxyuridae. Genus *Enterobius*, Leach 1853.

Enterobius vermicularis (*Oxyuris vermicularis*), the common pinworm or seat worm, has been known since ancient times. It is cosmopolitan in distribution, but is commoner in warm countries, probably because in these there is usually less attention by the people to personal hygiene.

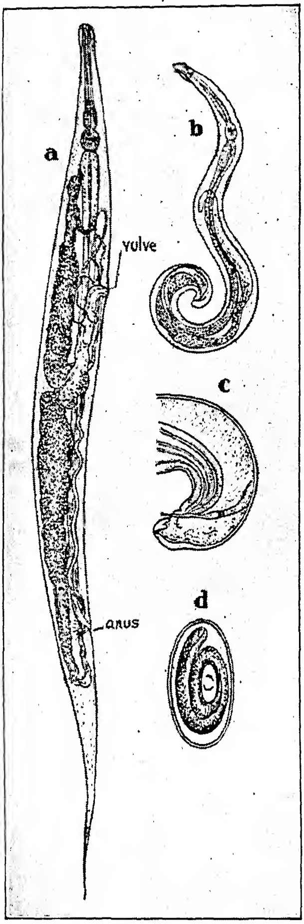


FIG. 275.—*Enterobius vermicularis*. (a) Female. (b) Male. (c) Coiled posterior extremity of the male showing the spicule. (d) Egg. (After Leuckart from Brumpt.)*

However, recent investigations carried on by the National Institute of Health, under the direction of Cram, show that it is very common in some temperate climates.

Thus a survey of various groups in Washington, D. C., showed an incidence of 35 per cent in over 600 persons examined by anal swabs. All positive cases found, but only part of the negative cases, were followed by examination of the families of which the individuals were members, since pinworm infestation is usually a familial affair, and commonly about three-fourths of the members of a family were found infested. The high incidence in Washington suggests that when pinworms are given greater attention in the United States it may be found that the situation here is in line with that stated by a number of well informed parasitologists, i.e., that pinworms are the most common and widely distributed of human helminth parasites. The parasite is found more frequently in children than in adults.

Cram (1937) and Smith and their associates (1939) in their survey in the Southern United States, found a somewhat heavier infestation rate among the males as compared with the females. Enterobiasis is more common in asylums and in infected groups or families, rather than in populations at large. Cram found, that an examination of 628 individuals in the general population group showed 35.4 per cent infested, while Smith, in an institution for mentally deficient, found the unusually high infestation rate of 65.15 per cent.

The eggs containing the embryos which are discharged by the female worm, usually after moving about outside the anus of infected patients, contaminate their clothing and fingers, especially beneath the finger nails. These eggs are the immediate source of infection and of most reinfections.

Morphology and Habitat.—The adult worms live in the caecum, appendix and adjacent parts of the colon and ileum, with their heads attached to the mucosa. The females sometimes invade the female genital organs and bladder and have also been reported in the ear and nose. The worms are small, and about the thickness of a piece of coarse thread. The white, squirming worm frequently may be seen on the surface of the faecal mass, or moving about the perineal region of the child. The female worm

* The shape of the egg is atypical in being so perfectly oval and without one side flattened.

often comes out of the anus when the child is warm in bed and the inspection of the perineal region may show the parasite. The male is about 2–5 mm. long, the female is larger, 8–13 mm. long by 0.1–0.2 mm. wide. The male has an incurved tail with a single spicule and the female a long tapering tail. The vulva is in the anterior third. These worms have a clear bulbous projection shaped like the mouth-piece of a Turkish pipe surrounding the three-lipped anterior extremity. There is a well-marked bulb-shaped oesophagus.

The eggs have a thin, double-contoured shell, are planoconvex, 20 by 50μ, and show a coiled-up embryo. After ingestion of segmented eggs the adults develop in the small intestine, where copulation takes place. The males disappear or die. The fertilized females usually go to the caecum and colon, where they remain until the ova have developed. The cycle occupies about four weeks. The females then wander to the rectum and work their way out of the anus to deposit their eggs on the skin of the perineum. Marked itching is a common symptom. This is more pronounced at night, and the scratching so induced causes the eggs to be widely spread about the region of the anus. The fingers thus become contaminated with ova which may be carried to the mouth and so cause a fresh infection. The underwear, bedding, towels, wash basins, floors, etc., are frequently contaminated. The possibility that the eggs may be air-borne has been shown. No intermediate host is necessary. About 36 hours outside the body in abundant oxygen is required for completion of development of the infective "tadpole" stage. If reinfection is avoided, the infection may die out spontaneously in a few weeks.

When the infective ova are swallowed, they pass to the duodenum, where they hatch and the larvae are set free. They then pass down the small intestine directly, (without migrating through the intestinal wall) and, after moulting twice, mature in the ileum or in the large bowel. The adult female worms not infrequently after passing from the anus invade the vagina and urethra and sometimes the prepuce.

Pathology

Faust (1940) has noted that the young males and females attached to the intestinal wall may produce mild catarrhal involvement of the immediate tissues where they reside and that in sensitive individuals their byproducts when absorbed may cause a characteristic helminthic toxaemia. Eosinophilia may or may not be present. Manson-Bahr (1940) reports that the mature worms may penetrate the mucosa and encyst in the submucosa of the small intestine or appendix, where they may give rise to inflammation.

A number of writers have recently reported instance of appendicitis due to Enterobius.

Battaglia has found the parasites in the appendix in 2 per cent of the cases of appendicitis in children when the organ was removed at operation, while Harris and Brown (1925) found Enterobius in 22 appendices out of 121 consecutive cases of operative appendicitis. Hippins and Levinson have reported the presence of Enterobius under the serosa of the appendix and in the contiguous lymph glands. Penso (1932) has pointed out these parasites may give rise to an appendicopathia by their movements, by temporary attachment to, or invasion of the wall, or by oviposition in the wall. While Ujiie, 1935, points out they may allow pathogenic bacteria to enter the mucosa of the appendix. Botsford (1939) reports that 71 of 1343 appendices removed at Children's Hospital, Boston, 1929–39, were infected with pinworms. Twenty-six had acute appendicitis and pinworm infection. Forty-five had no inflammatory change in the appendix, but had pinworm infection. All had abdominal pain and all were

relieved by appendectomy. Schwarz and Straub (1940) have also emphasized the importance of oxyurids in appendicitis with purulent inflammation. Ashburn (1941) has found that thread worms are encountered in normal appendices, as well as in those which show chronic inflammatory changes, and more often than in those that are acutely inflamed. In the study of a large series by sections he came to the conclusion that these parasites are not etiologically related to appendicitis.

Africa (1938) has emphasized disturbances occasionally caused by the gravid females migrating up the vagina and uterus into the fallopian tubes, where they have become either encysted in this organ, causing symptoms of salpingitis, or continue their wandering into the peritoneal cavity, where they have become encysted in the peritoneum.

Jones and Bunting (1931) have reported the case of a woman 22 years old with a history of prolonged perineal nocturnal itching and with symptoms of pain and tenderness in the lower part of the abdomen, accompanied by fever and leucocytosis. Laporotomy revealed acute appendicitis and acute salpingitis with *Enterobius* in both organs. Africa points out that the presence of these worms in the abdominal cavity has been invariably reported in the *female* subject, and since numerous reports of the presence of this parasite in the vagina, uterus and fallopian tubes have been made, it seems clear that the route usually taken by Enterobius in its migration to the abdominal cavity is via the genital tubes from the anus. Wu (1935) has shown that they may produce symptoms of salpingitis which may continue for years.

Blacklock (1938) has pointed out that the eggs can sometimes be obtained from the washing of infected garments and Lentze maintains that the ova can be inhaled through the nose at some distance from infected garments.

Symptomatology.—In addition to the symptoms resulting from the pathological changes already described, pin worms commonly give rise to pruritus ani which provokes scratching of the irritated parts, sometimes resulting in haemorrhage, eczema, and pyogenic infection of the anal and peri-anal regions or of the entire perineum. The abrasions of the mucosa of the caecum by the parasites may expose nerve endings and give rise to nervousness, insomnia, and even epileptiform seizures, especially in children. Masses of the parasites in the rectum may give rise to symptoms of rectal colic. Sometimes the adult females may pass up the bowel wall into the upper portions of the small intestine and may eventually reach the stomach, oesophagus, and nostrils.

Diagnosis

Ova are rarely found in the faeces, but may be found in scrapings from the skin about the anus, or from under the nails. The diagnosis is preferably made by examining the stools for the white, thread-like females which are expelled after a diagnostic dose of calomel and salts or after an enema. These females, which are packed with embryo-containing eggs, may be seen wriggling on the surface of the freshly passed faeces. In handling these worms, care must be taken to avoid infection with eggs, which may get on the fingers.

The diagnosis may be made by finding the ova in the faeces or in scrapings or swabs made from the perianal region or beneath the finger nails. It may also be made from the finding of the adult worms, especially following enemas, or of discovering the female parasites wandering out of the anus, which particularly occurs at night. The eggs have been found

in the faeces, usually in not over 5 per cent of the cases (Faust, 1940; Africa, 1940).

Diagnosis of the infection has been greatly simplified by Hall (1937) and his associates, who have recommended and used a cellophane anal swab.

Smith, Gill and McAlpine (1939), Sawitz, Odom and Lincicome (1939), and Ruhe (1940) have all emphasized that the cellophane swab is much more successful in giving a positive diagnosis than the direct examination of the stools or of concentrated faecal films. They point out that it is also of much greater value than the previous swabs recommended.

Smith has shown that the salt flotation method of examination of the stools is neither accurate nor dependable for finding *Enterobius* eggs. He found 99.5 per cent of the cases were positive by the swab method, whereas only 3.9 per cent were positive by salt flotation.

Of 400 positive examinations by anal swabs, 73.6 per cent were found on the first examination and the remaining 26.4 per cent after 2 or more examinations. Other observers, however, recommend that at least 7 consecutive swabs should be taken before a suspected case is diagnosed as negative.

Reardon (1938) has pointed out what to the uninitiated might cause confusion, namely that artifacts which simulate ova of enterobius may be present in the cellophane of the NIH swab described by Hall for use in the diagnosis of pinworm infection. The structures are markedly similar to the pinworm egg. The hyalin outline appears to be composed of several layers and resembles the transparent shell of the egg of Enterobius. The central mass is irregular, brownish or greenish, the size usually falls within the range of the pin worm eggs.

Treatment

A knowledge of the life history—the early location in the small intestine and later on in the large—shows that treatment should be dual in its direction—enemata to remove the gravid female in the rectum and anthelmintics to destroy the young adults in the small intestine. Some still question whether an entirely dependable therapy for pinworm infestation has yet been developed.

High enemas frequently remove the majority of the free females in the colon. For this purpose infusion of quassia diluted 1–40 has been frequently employed, the solution being injected slowly and the foot of the bed raised so as to allow it to percolate through the bowel. It is advisable before administering the quassia to evacuate the rectum first by hot water enemas. However, such treatment frequently does not succeed or remove the new groups of parasites which are developed higher up in the bowel.

For the destruction of these parasites many anthelmintics have been recommended by one author or another, but most of them have proved valueless. More recently Wright (1938), has recommended tetrachlorethylene. The recommended dosage is 3 cc. for an adult, 3 minims per year of age for children. Purgation of the patient should be obtained the night before, preferably by the use of sodium sulphate, 30 gms. in a half glass of water. In the morning the patient should abstain from food before the drug is taken. Two hours after administration of the drug a saline purgative should again be administered. Poisoning has sometimes resulted from the use of this drug. Sandground (1941) mentions 2 cases of coma when doses of 4 to 5 c.c. were given.

Faust (1940) states that this treatment while at times quite satisfactory is not consistently so. He believes that a relatively satisfactory method of treatment consists of the administration of caprokol (Hexylresorcinol crystoids), 1 gm. for adults, 0.6–0.8 gm. for children, on an empty stomach in the morning.

The patient is required to swallow the capsules without chewing and to fast subsequently for 5 hours. The same night the large bowel is thoroughly washed out with a warm-water enema, after which 250 to 400 cc. of "S.T. 37," a solution of hexylresorcinol (0.1 per cent), is instilled as a retention enema and retained for 15 to 30 minutes. The crystoids given by mouth kill the worms in the small intestine, while the solution instilled into the colon cleans out the female worms in the lower bowel. Two or three such courses of treatment usually completely eradicate the infection, provided reinfection is not acquired in the meantime. Cutaneous lesions around the anus, produced by scratching and frequently aggravated by bacterial invasion, should be treated by palliative or antiseptic ointments like borated vaseline or yellow mercuric oxide.

Still more recently, Wright and his associates (1940) and D'Antoni and Sawitz (1940) have recommended the oral administration of gentian violet medicinal for treatment in ½ grain enteric coated tablets manufactured by the Seal-Ins Laboratory and by Ely Lilly & Co. They employed tablets of the four-hour type which are said to dissolve in the caecal region when administered. Treatment of infected boys and girls with this drug resulted in the cure of approximately 90 per cent of the cases. The drug was administered to infected individuals from 3 dormitories.

In the first dormitory the adult dose recommended by Wright was employed, namely 1 grain of the drug was given 3 times daily before meals for a period of 8 days, followed by a 7 day, medication-free period, after which the 8 day course of treatment was repeated. In the second dormitory 1 grain of the drug was given 3 times daily before meals for a period of 5 days, followed by a medication-free period of 3 days. This procedure was repeated until 20 days of treatment (i.e., 4 five-day courses of treatment) had elapsed, making the entire period 29 days. In the third dormitory, ½ grain of the drug was given 3 times daily before meals continuously for a period of 35 days.

After such treatment, swabs showed that 94 per cent of the positive cases in dormitory I, 90 per cent in dormitory II, and 89 per cent in dormitory III were free of pinworms.

The drug was found in general to be well tolerated. However, of those who took 1 grain of gentian violet 3 times a day, more than half (54 out of 95) complained of loss of appetite, abdominal cramps or nausea at one time or another, whereas of those who took ½ grain 15 out of 45 complained of these symptoms. Vomiting occurred in a high percentage of those treated with uncoated gentian violet tablets.

In a more recent report, Wright and Brady (1939) point again to the efficacy of this drug, tested on 224 persons. It was given in daily doses of 192 mgm. for adults before meals and to children 10 mgm. a day for each year of apparent, not actual, age. When treatment was pursued for 10 consecutive days, unworming was effected in 91 per cent. In a series which had 2 stages of treatment for 8 days, with a week's rest between, the unworming was 90 per cent. Some of those treated had nausea, vomiting, diarrhoea and abdominal pain which quickly ceased when treatment ceased for a day or two. They found non-medicated soap or saline enemas might be satis-

factory in infants and young children if given every other night for not less than 3 or 4 weeks, but the course had often to be much longer.

Manson-Bahr (1941) has stressed the use of phenothiazine for the treatment of thread worms. Children from 5 to 10 years old receiving 15 grains daily for at least 10 consecutive days and for children under 5 years, the dose is halved.

Errington has noted toxic symptoms in the treatment of horses with this drug, such as anaemia, albuminuria, and haemoglobinuria and later work seems to show that its use in man is dangerous.

Johnstone (1942) points out that in 58 published cases of treatment with phenothiazine for thread worms, 8 showed some form of toxic reaction. He hence considers that this use of the drug cannot be justified.

Bercovitz, et al. (1943) treated 10 patients, children and adults, for enterobius infections with phenothiazone. Two patients were considered cured; the others were not. Most (1943) believes that phenothiazine should be given only to patients who cannot be cured by gentian violet or who are intolerant to it. It should not be given to patients who cannot be observed once every 3 days. He advises the dose of phenothiazine should not exceed 300 mgm. per kgm of body weight. He himself safely and successfully used this dose for 22 of his patients.

Prevention.—Personal hygiene is definitely indicated for the prevention of reinfection. Sleeping drawers of strong cotton and cotton gloves at night should be worn. The finger nails should be carefully pared and the hands washed after defecation. To prevent itching at night, the anus may be anointed with mercurial ointment, or unguentum hydrarg ammoniat. Clothing of the infected should be periodically sterilized by boiling. Toilet seats should be regularly scrubbed and sterilized in families or homes where one member is infected.

Nevertheless the work of D'Antoni and Sawitz demonstrated that it was impossible to entirely exterminate the infection, or even to prevent infection in other individuals, by rigid hygienic measures carried out in an institution. Only by treatment with gentian violet, in addition to the employment of hygienic measures, could the infection be eradicated, 90 per cent of the cases being cured. They emphasize that treatment of the infected individuals alone will not suffice to rid an institution of oxuriasis, since if a single infected individual remains he constitutes a serious problem and suggests a probable source of reinfection.

Nolan and Reardon (1939) found the eggs of *Enterobius* in dust collected at all levels in all the rooms of 7 houses in which lived infected persons. They believe infection of air currents is theoretically possible.

TRICHURIASIS OR TRICHOCEPHALIASIS

Trichuriasis, or Trichocephaliasis, is caused by the whip-worm, *Trichuris trichiura* of the superfamily *Trichuroidea.*

It is characterized by a long, thin neck and a thicker terminal portion. The oesophagus consists of a narrow tube with reduced musculature. It has a thin wall and is apposed to a single row of large secretory cells. The anus is terminal. There is only one ovary.

The families TRICHURIDAE and TRICHINELLIDAE are distinguished by the latter being much smaller, not having a spicule, and copulatory sheath, and being viviparous.

Genus Trichuris (Roederer, 1761).—*Trichuris trichiura; (Trichocephalus*, Schrank, 1778) *Trichocephalus dispar*, Rudolphi, 1802, the whipworm, is one of the most common parasites in both temperate and tropical climates. It gets its name from the resemblance to the whip, the posterior end resembling the handle and the anterior extremity the lash. The species was first correctly named by Linnaeus in 1771. The life cycle was demonstrated by Grassi (1887) and later by Fülleborn (1923).

Geographical Distribution.—The parasite is cosmopolitan in its distribution, but is more common in tropical regions where the warmth and humidity contribute both to the incidence and the intensity of the infection.

Cort (1938) points out that while whipworm infection is more or less co-extensive with that of *Ascaris lumbricoides*, the former is more prevalent in areas with high rain-fall and humidity and dense shade.

Morphology and Biology

The worms are 30 to 50 mm. long, the females slightly longer than the males. The cephalic half to two-thirds of the body is thread-like and contains only the oesophagus. This has a reduced musculature and is apposed to a row of large secretory cells, the stichocyte, which communicate with the lumen of the oesophagus by small apertures. The thick caudal portion of the body (the handle of the whip) contains the intestine and sex organs. The tail of the male is coiled and ends in a single terminal spicule surrounded by a rough sheath. The tail of the female is comma shaped. The vulva opens at the cephalic end of the thickened segment of the body.

The worms are found chiefly in the caecum, also in the appendix and terminal ileum. They attach themselves to the intestinal wall by transfixing a fold of mucosa with the

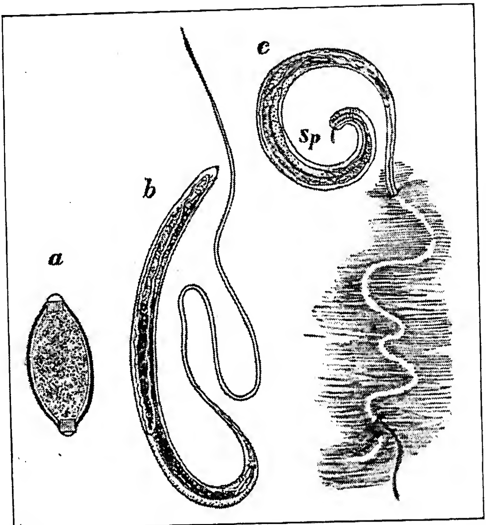


FIG. 276.—*Trichuris trichiura.* (a) Egg. (b) Female. (c) Male with neck embedded in mucous membrane; sp. spicule. (After Leuckart.)

slender neck and have been thought by some to facilitate the entrance of typhoid bacilli and other pathogenic bacteria into the tissues. The characteristic ova are deposited in the faeces. They are oval structures 22μ by 50μ, brown in color, with unsegmented granular contents and a thick translucent capsule which has a knob-like protrusion at each end, somewhat like a bottle stopper. Segmentation occurs outside the body and is a protracted process, requiring from 6 weeks to (it is said) 18 months. The ova are resistant (except to desiccation) and have been reported to have retained their infectivity for 5 years. There is no intermediate host.

Infection occurs by swallowing infective ova obtained directly or indirectly from the soil. Areas in which there is a high incidence of infection are usually polluted by small children, who are more commonly infected than are adults. The parasite matures about one month after infection.

Pathology

The infection is usually symptomless. Craig and Faust (1940) point out that worms may not only be attached by their anterior ends to the

intestinal wall but interlaced in the mucosa where, according to Hoeppli (1930) they may secrete lytic substances. Chitwood (1937) and others believe they may possibly suck blood. It is believed that they may sometimes cause attacks of urticaria. According to Faust, in heavy, uncomplicated whipworm infection the patient may show marked emaciation, with a dry skin and mucous diarrhoea, rarely with blood, and a reduction of the haemoglobin which may reach 40 or 50 per cent. Pallister (1933) has reported masses of worms extending as far down as the ascending colon. Clinically such cases may suggest severe hook worm disease and it is said patients so parasitized may soon succumb unless the worms are removed. Swartzwelder (1939) has studied 81 cases uncomplicated by other infections.

In most of the cases the infection was heavy. More than two-thirds of the patients fell within the age group from 6 to 15 years. White patients predominated over the colored in a ratio of 5 to 1, and females over males in a ratio of 2 to 1.

The most frequent symptoms were abdominal or epigastric pain, vomiting, constipation, fever, distention or flatulence, headache, backache, loss of weight, and anorexia. Abdominal or epigastric pain was the most frequent complaint, noted in 59 cases. The duration of the symptoms in 44 cases was 3 months or less. In a number of the cases, the abdominal pain was localized in the right lower quadrant with nausea, constipation and fever, suggesting appendicitis. No marked diminution of the red blood count was noted and this is in accord with Otto's studies in Louisiana in 1934. Swartzwelder found the eosinophiles averaged 4.2 per cent, with 24 per cent the maximum.

However the number of eosinophiles varies greatly. Otto believes it is probable that no eosinophilia is produced by chronic whipworm infections, though there may be an eosinophilic response to acute ones. Fernan-Nunez, however, found that eosinophilia is more constant in whipworm infection than with other nematodes. In about one-fourth of the cases a mild leucocytosis occurred. In only 7 cases was the temperature elevated above 101°F.

Diagnosis

The diagnosis can be made by finding the ova in the stools. Concentration by centrifugation or brine flotation as described under Ascaris may be necessary to reveal their presence in mild cases.

Treatment

Treatment is not always satisfactory. The drug which has been said to be most efficacious in the eradication of the parasite is *Leche de higueron*, or higuero latex, obtained from certain species of trees of the genus *Ficus* in Central and South America. The active principle is an enzyme which has been extracted from the fresh latex or sap by Robbins (1930) and was named ficin. He concluded that the active fraction was a proteolytic enzyme of the tryptic type. Favorable reports of its use have been made by Spruit (1921), Hall and Augustine (1929), and Caldwell and Caldwell

(1929). However, in not all instances has complete eradication of the worms resulted.

Robbins and Lamson (1934) have tested the enzyme action of 15 species of the genus *Ficus* from Cuba and *F. carvea* from Alabama, but found that the proteolytic activity of all except two of the species tested was essentially nil. However, they found that the sap of 6 *Ficus* trees of South America had a high proteolytic activity. Recently Thomen (1939) has recommended a more refined product, "Ficus protease," prepared by Bliss. This preparation was found by Thomen (1939) to be highly efficient as an anthelmintic against *Trichocephalus vulpis* infection in dogs. Unfortunately, the latex itself, *Ficus*, does not keep except in a cold atmosphere and is not generally available commercially for anthelmintic use. In Mexico, Central America, and North and South America, the fresh latex is preserved with 1 per cent sodium benzoate and is sold under the trade name Higueronia. However, Faust (1941) thinks the fresh crude latex is better.

Other drugs which have been recommended for treatment are carbon tetrachloride, tetrachlorethylene, oil of chenopodium, and hexylresorcinol. These drugs, however, may produce toxic symptoms. Carbon tetrachloride is contraindicated in patients with hepatic, renal or respiratory involvements, those with fever, and in those having a blood serum calcium deficiency. Faust also cautions that carbon tetrachloride should not be administered alone when *Ascaris* is present though it may be combined with oil of chenopodium, see p. 1270. Oil of chenopodium is more toxic than carbon tetrachloride.

Recently Mackie (1939) and Smillie (1939) have pointed out the value of hexylresorcinol as an anthelmintic.

For hexylresorcinol treatment, preliminary purgation is desirable to free the caecum and appendix of faecal material.

Hexylresorcinol crystoids ("Caprokol") are best given on an empty stomach and followed within 2 hours by a saline purgative. For small children under 6 years, 0.4 to 0.6 gm. is indicated, and for children of school age the adult dosage of 1 gm. may be administered. It is advised that the drug should be swallowed in water without breaking or chewing the crystoids to avoid irritation of the mucosa of the mouth and throat. Food should be omitted for 5 hours to alleviate and prevent irritation of the gastric mucosa. It is advisable that the large bowel should be cleaned out with tepid water enemas on the night following administration of the drug. Faust recommends also that 8 to 12 oz. of S.T. 37 (hexylresorcinol 1–1000) undiluted be introduced for 15–20 minutes as a high retention enema. Examinations of the stools should be made for ova from 3 to 5 days after the treatment has been administered to determine the efficiency of the drug. A second treatment with hexylresorcinol may be given within a week if necessary.

Prevention.—Thorough cleaning of the hands before meals may do much to reduce both the incidence and intensity of the infection. Cases should be treated as soon as possible after diagnosis. There should be disinfection and sanitary disposal of faeces, as is recommended for hookworm infection.

TRICHINOSIS

Definition.—A parasitic disease caused by *Trichinella spiralis*, sometimes characterized by fever, gastro-intestinal symptoms, myalgia, and eosinophilia, the infection occurring in individuals who have ingested raw

or insufficiently cooked pork. Many cases of infection do not develop any striking clinical symptoms and evidence of the parasite is only found by post-mortem examination.

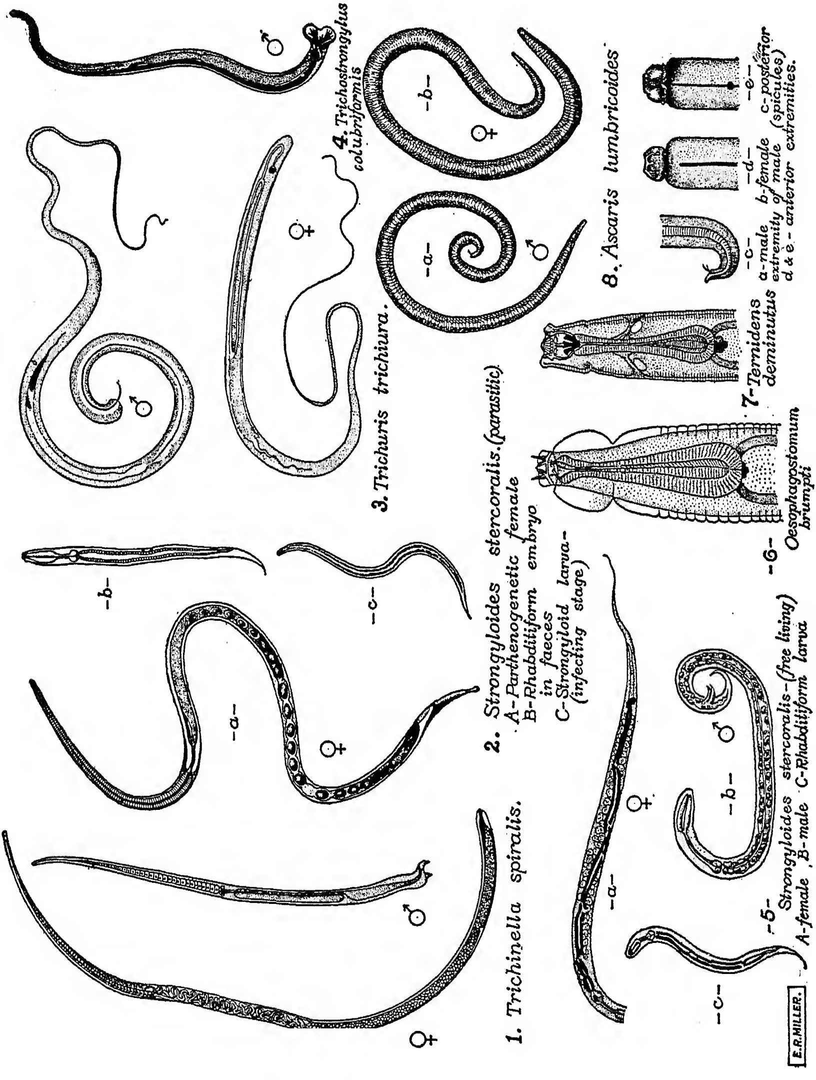


FIG. 277.—Some of the human nematodes.

Geographical Distribution.—The distribution of *Trichinella* is cosmopolitan. It has been especially prevalent in Germany and in earlier years Virchow estimated the human incidence in that country as about 90 per cent. Although it is still stated to be widely distributed in Germany and to a less extent in Spain, Hungary, and the lower Danube countries, exact statistics at the present time are not obtainable. In the United States it is common. Hall and Collins, 1937, have reported the incidence of trichinosis from 11 widely scattered cities in the United States, based on actually finding the parasites at autopsy, as 12.5 per cent of 1778 unselected cases, or one out of every

8 examined. Scheifley (1938), in the examination of published reports regarding trichinosis in the United States since 1901, finds that in 2597 postmortem examinations there was an incidence of trichinal infection in 12.3 per cent. Examination of the diaphragms from 200 autopsies in San Francisco in 1935–1936 showed that 24 per cent were positive for living *Trichinella* larvae and in New York State, for 1936, in 344 consecutive autopsies in Rochester 17.5 per cent of the diaphragms contained *Trichinella spiralis*. Other post mortem examinations in St. Louis showed a 15 per cent incidence, and in Minneapolis according to two surveys a 12.7 and a 17.9 per cent incidence. By peptic digest methods, which yield a higher percentage of positives than microscopic sections, Queen (1931) found 27.6 per cent incidence in Boston, and a 13.67 per cent incidence was found in Maryland and Washington (Hall and Collins, 1937). Although it has been stated that *clinical* cases are rarely reported from the southern United States, and this is also true in a number of the northern states, Sawitz (1939) found a 6 per cent incidence among *autopsy* cases in New Orleans and Walker (1938) has reported a 33 per cent incidence in post mortem examinations in Alabama.

Wright (1938) summarizes the results in the United States as roughly 17–18 per cent of infection.

The reports of clinical cases for the United States up to 1937 number between 5000–6000.

In regard to tropical and sub-tropical countries, sporadic infections have been reported in South America, especially from Brazil and Chile. In Asia, it is not uncommon in China and India but is not reported from the Philippines. Cases have been reported occasionally from Australia (Manson-Bahr, 1940), but according to Bearup (1937) it is probably not endemic in Australia. It does not occur or is rare in Puerto Rico or in Mohammedan countries. In Africa, it has been reported in Algeria, Kenya, Uganda, Tanganyika, and British Nigeria.

Sandground (1941) says the disease is at present restricted to Europe and North America but occurs in immigrants elsewhere or in those who have eaten imported infected pork products.

History.—*Trichinella spiralis*, the cause of trichinosis, was first discovered in the encysted stage in the muscles of patients at post mortem examinations in London by Peacock (1828). Human cases were soon reported also from Europe and North America. Joseph Leidy, having found for the first time the cysts in hogs' flesh in 1846, suggested their similarity to those found in man. Leuckart (1855) and Virchow (1859) demonstrated that these cysts, when fed experimentally to animals, the parasites were liberated and grew into adults in a few days and that the females in the duodenal wall produced larvae which migrated to the muscles and there became encysted. Later it was shown that the consumption of infected pork, insufficiently cooked or raw, was the source of trichinosis in man.

Thomas R. Brown, in 1897, while a medical student at Johns Hopkins, demonstrated that the presence of an eosinophilia is highly suggestive of a diagnosis of trichinosis.

Trichinella spiralis (Owen, 1835) (*Trichina spiralis*), the cause of trichinosis, is a minute worm, visible with an ordinary hand lens, which in its adult stage inhabits the duodenum and jejunum. The *male* is about 1.5 mm. long and 40μ wide. There is a prominent testicular enlargement filling the wider caudal end of the body and two tongue-like caudal appendages which project laterally and enable the male to hold the

female during copulation. There is no spicule, and the cloaca is evaginated to act as a copulatory organ.

The *female* is 3 to 4 mm. long and 60μ broad and has a rounded posterior extremity with a prominent slit-like cloaca. The posterior half of the body contains the ovary and becomes swollen as the eggs develop. The vulva is in the anterior fifth of the body. After copulation the males may die, and the viviparous females burrow into the intestinal mucosa and for about 6 weeks continue to emit living larvae, each producing a number estimated at from 1000 to 10,000 in all.* The larvae are about 100μ by 6μ in size. They penetrate into lymphatics or veins and are distributed through the general circulation. They soon penetrate into striated muscle, being especially numerous in the diaphragm, intercostals, and muscles of the neck, larynx, tongue and eye. Here they become *encysted larvae*, forming oval structures about 0.45 by 0.25 mm. in size. They are surrounded by a tough capsule produced by the tissues of the host, while the larva, which has attained a length of 1 mm., is coiled up in the center. Here they remain viable for a long time (some even for 10 to 20 years) although the larva eventually dies and the cyst becomes calcified. When the cysts are swallowed the larvae are liberated in the intestine and within a few days develop into mature adults. This parasite, therefore, differs from practically all other nematodes in that the larvae encyst in the same individual host which harbors the adult worms.

Transmission.—Man usually becomes infected from eating raw or improperly cooked pork. Under natural conditions, the infection chiefly affects rats and hogs. Hogs become infected especially by eating garbage containing pork scraps and to a less extent infected rats, and rats by eating scraps of pork and by cannibalism among themselves. The infection is normally propagated by the black and the brown rat, both of which are cannibalistic.

In an examination made in St. Louis, Mo., 75 per cent of the rats were found to be infected. Many other animals, however, are also susceptible, as wild boars, bears, cats and dogs. Other animals, as mice, rabbits and guinea pigs, are easily infected when fed raw meat containing the parasites. While in America, hogs are most commonly infected, in some localities in Europe dogs and cats have shown a higher percentage of infection than hogs. In general, the incidence in hogs has been stated to be about one fifth that in man. Man not only acquires the infection by eating raw or inadequately cooked pork but sometimes through bear's meat. In Syria, outbreaks have been reported from eating the meat of wild boars.

Symptomatology and Pathology.—The symptoms of the disease vary greatly and the picture of clinical trichinosis is frequently most confusing. This, however, is not surprising when one considers the wide-spread distribution of the parasites that may occur in different parts of the body, for the larvae have been found in almost every tissue, fluid and excretion, even though those which do not enter skeletal muscles usually die rapidly. Ransom (1915) emphasized that an important characteristic of trichinosis, whether mild or severe, was the lack of regularity of its course. Symptoms depend partially upon the number of worms present and partly upon the tissues invaded, as well as upon the stage of the infection. In regard to the latter, to begin with, the infected larvae enter the digestive tract and develop into adults in the lumen of the intestine, where they lie partly within the villi. Later they give rise to young larvae, circulating through the lymphatics to the systemic and pulmonary circulation and entering such tissues as the lymph nodes and glands, the brain, the muscles

* Rappaport (1942) finds the males may outlive the females.

of the heart and all other muscles, and to some extent other tissues and various cavities of the body. Finally we must consider the effects of the larvae degenerating and disintegrating in various sites and becoming encysted and ultimately calcifying in such locations.

With reference to the number of *trichinae* present giving rise to clinical symptoms, we have no accurate data. Hall (1937) states that he feels sure that necropsy cases of infestation of approximately 1000 larvae per gram diaphram muscle represent former cases of clinical trichinosis and he suspects that those with only 1 larva per 100 grams of diaphram muscle probably do not represent cases of clinical trichinosis (with symptoms).

Gastro-intestinal disturbances are often noted in the first stage of the infection. Manson-Bahr points out that such symptoms may resemble those occurring in cholera, or even in dysentery, with the passage of blood-stained stools associated with hyperpyrexia. In severe cases, during the migration of the larvae through the tissues, there may be a remittent temperature with slow muttering delirium, muscular pains, pain on mastication, and disturbances of deglutition and respiration. The condition may suggest typhoid fever. Several weeks after infection, when the embryos have encysted in the muscles a cachectic condition may result, due perhaps to the absorption of toxins from the parasite, when, in addition, oedema of the face, abdomen and legs may occur. In other instances there may be mental apathy and intense pruritis. Death may take place in the sixth or seventh week from exhaustion or from pulmonary complications. In cases which survive, the fever gradually declines but pains in the muscles may persist for long periods. While such symptoms may be regarded as the classical picture of the disease, even in severe trichinosis, many or all these symptoms may be omitted.

Hall (1937) gives the following list of symptoms and the diagnoses which have been associated with the effects of the parasite in several locations, rather than in just the location given:

Larvae and Adults in Intestinal Lumen and Villi. *Symptoms.*—Gastro-enteritis, diarrhoea, constipation, or successive constipation and diarrhoea, "vegetable-soup stools," often with Charcot-Leyden crystals, nausea, vomiting, abdominal pain of varying degree and in various locations, cold sweats, hot flushes, intestinal haemorrhages, and fever; *diagnosed* as typhoid fever, paratyphoid fever, typhus fever, cholera, cholera morbus, intestinal influenza, malaria, ptomaine poisoning, food poisoning, gastroenteritis of unknown origin, gastro-intestinal catarrh, appendicitis, colitis, peptic ulcer, gall bladder involvement, and acute alcoholism.

Larvae in Blood Stream and Muscles. *Symptoms.*—Eosinophilia, oligaemia, oligocythaemia, hypotension, leucocytosis, splenic enlargement, anaemia absent or else present in varying degree, oedema in various parts of body (especially suborbital), dyspnoea, orthopnoea, diaphragmatic breathing, pleurisy, cough, hiccough, asthma, haemoptysis, pneumonia, dysphagia, aphonia, laryngitis, myositis, myalgia, furunculosis, cutaneous eruptions, urticaria, rose spots, desquamation, sweating, apathy, lassitude, somnolence or insomnia, anorexia, conjunctivitis, corneal ecchymoses, mydriasis, photophobia, diplopia, pulse often slow by comparison with height of fever, albuminuria, present or absent, indicanuria present or absent, positive diazo reaction, casts in urine, positive Kernig's sign, loss of patellar and Achilles' tendon reflexes, neuritis, rigor, persistent or remittent fever. and menstrual disturbances; rea*gnosed* as arthritis, rheumatism, rheumatic fever, dermatomvositis, pevic inflamma-

tory disease, pleurisy, asthma, upper respiratory infection, pneumonia, laryngitis, conjunctivitis, nephritis, multiple neuritis, intercostal neuritis, angioneurotic oedema, syphilis, tuberculosis, undulant fever, tetanus, scarlet fever, measles, mumps, influenza, frontal sinusitis, erysipelas, and lead poisoning.

Larvae in Heart. *Symptoms.*—Myocarditis, systolic murmur at apex, cardiac instability, and dicrotic pulse; *diagnosed* as myocarditis, rheumatic myocarditis, endocarditis, or other heart diseases.

Larvae in Brain and Meninges. *Symptoms.*—Encephalitis, meningitis, cephalalgia, hemiplegia, delirium and coma; *diagnosed* as encephalitis, meningitis, tuberculous meningitis, and poliomyelitis.

Even in severe clinical trichinosis, the first stage of gastro-intestinal disturbances has frequently been absent. Eosinophilia also may be absent, especially if there is a concomitant bacterial infection, or may decrease if bacterial infection supervenes. Again, if peritonitis is present the eosinophiles may never rise above 3 per cent. While there is usually a gradual rise followed by a gradual decline, the level may never be high and the eosinophilia may persist for long periods after recovery. The myalgia may be generalized, or definitely localized. In some instances the clinician may be misled and diagnose it as intercostal neuritis or neuritis elsewhere, or refer it to rheumatic conditions. Ocular disturbances, as well as cardiac and nervous changes suggestive of meningitis, may all be confusing factors.

Briggs, Bruck and McNaught (1939) have called attention to "splinter haemorrhages" seen beneath the finger and toe nails in 60 to 70 per cent of their cases of active trichinosis. McNaught regards it as a petechial manifestation similar to rose spots on the abdomen, described by others.

In severe epidemics, the mortality may reach 30 per cent. Chandler (1940) remarks that it has been estimated that for man the ingestion of 5 trichina larvae per gram of body weight for man is fatal, for hogs 10, and for rats 30.

Diagnosis.—The great majority of human infections are not diagnosed during life, the correct diagnosis being frequently made by microscopical examination of sections of the diaphram or other muscles or of material obtained by artificial digestion of them after death.

Hall and Collins have pointed out that in not one of 222 infections found postmortem had a diagnosis of trichinosis been made during life, although in some there were almost 1000 parasites per gram of muscle and obviously any person harboring that many trichinae could not have been entirely free of symptoms. The difficulties in clinical diagnosis have been emphasized.

Too much weight must not be attached to any one symptom. A history of eating raw or undercooked pork, gastro-intestinal disturbances, oedema, petechiae, fever, myositis, and eosinophilia are suggestive symptoms. However, accurate diagnosis can be made only from the laboratory examinations.

Laboratory Examinations.—During the first few days after infection, while the ingested larvae are developing, there is often a gastro-enteritis. Purging then may be beneficial by ridding the intestine of the infected

pork and of some of the parasites. The adults can occasionally be found (but usually are not) by repeatedly suspending the faeces in water and decanting, and examining the sediment with a hand lens. On the whole, however, the examination of the stools for trichinae is not at the present time regarded as a valuable aid to diagnosis, and Hall (1937) states that the weight of evidence is to the effect that it is of little if any value.

As other aids in diagnosis, there are the search for trichina larvae in the blood and cerebro-spinal fluid, the *skin test* and precipitin test, and the biopsy method for the examination of excised tissue. As regards the blood and cerebrospinal fluid examination, the larvae may be present beginning a week after infection, although they are not always easy to find. The cerebro-spinal fluid should be centrifuged and the sediment

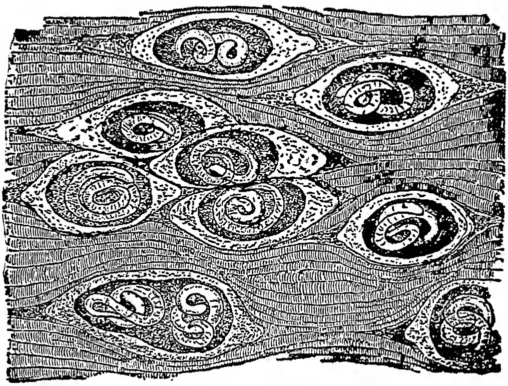


FIG. 278.—*Trichinella spiralis*. (Ziegler.)

examined. They may persist in such locations throughout the period of larval production by the females in the villi and have been detected in the blood in some instances over a period of 3 weeks. Also, it must be borne in mind that when they are looked for too early or too late they will be absent, even if the case is clinically trichinosis. The biopsy method has the limitation that it is negative in the early stage of the disease, and even when trichinae have just arrived in the muscles they are much less likely to be detected than when they have had time to grow and encyst. However, this examination is often very valuable in diagnosis and gives dependable information provided the biopsy specimen comes from an infested muscle. In connection with the examination of the muscle of the patient, it is advisable, if possible, to secure some of the suspected meat eaten and also examine it for encysted larvae. The specimen from the patient or animal may be teased or pressed into a thin layer between heavy glass slides and examined with the ⅔ inch objective. If no cysts are found, chop up some of the meat and digest over night at 37°C. in artificial gastric juice (0.7% pepsin in 0.3 per cent HCl). Then put the material in the Baermann funnel apparatus and after a few hours examine the fluid in

the stem of the funnel for larvae by means of the microscope (2/3 inch objective).

Also, some meat may be fed to several white rats or mice. After 2 or 3 days examine the duodenal contents of one animal for adult worms. After two weeks examine the muscle of the diaphragm etc. for encysted larvae as above.

During the second and third week in severe cases when there is high fever, marked intoxication and prostration, as in typhoid fever may occur. There is often transient oedema, especially about the face and eyes. There is usually a high leukocytosis with a *marked eosinophilia*, although this may be absent in the early stages and in fulminant cases. The *larvae* are then present *in the circulating blood.* To demonstrate them withdraw about 5 cc. of blood and lake in 3 volumes of 3 per cent acetic acid. Centrifugalize and examine films of the sediment stained by Giemsa's method.

From the tenth day on, the larvae begin to migrate into the muscle and become encysted. This is associated with severe pain, stiffness and disability. There is often painful labored breathing, laryngitis with cough and occasionally haemoptysis. After this time *excise a bit of muscle* from the deltoid or pectoral muscle near its insertion, and examine for encysted larvae, as described above.

Cutaneous Reactions.—Bachman (1928) reported positive precipitin and intracutaneous reactions in infected animals, using an antigen which he obtained by digesting heavily infected muscle in pepsin and HCl and by washing, drying, grinding and extracting the larvae so liberated. Coca's solution may be used for extraction. A commercially available *Trichinella* antigen is prepared by Eli Lilly and Co.

The intradermal test has been applied successfully to the diagnosis of human infection, by Augustine and Theiler and Spink and McCoy et al. (1933), who obtained (in Rochester, N. Y.) positive reactions (the immediate production of a large wheal) in 92 per cent of 36 acute cases and in 60 per cent to 80 per cent of cases from 3 months to 7 years after infection. They gave 0.1 cc. of a 1 to 10,000 and if this is negative, a 1 to 500 dilution. Late reactions occur, but McCoy found them unreliable in human infection. In most cases the reaction became positive during the third week. In a control series 18 per cent gave positive reactions, which is practically the incidence of infection found by Queen (1931) in a special study of 344 routine autopsies (also in Rochester, N. Y.).

Kalgus (1936) in Puerto Rico, found a positive skin reaction in 74 per cent of 66 cases of trichinosis which might seem unusual in that locality. McNaught (1939), in San Francisco, tested 63 individuals and found 12.7 per cent who gave the immediate type of reaction and 11.9 per cent a delayed type of reaction. There was no history of infection in McNaught's cases. Schapiro, Crosby and Sickler (1938) performed routine intracutaneous skin tests by Bachman's method on 400 individuals. Of these, 116 died in which the reaction in 27 had been positive, and in 89 the reaction negative. Only 3 of the cases found to be positive to the skin test were found to be negative for trichina infection at the autopsy. Autopsy records in San Francisco have shown that 24 per cent of the diaphragms may contain living trichina.

Failmezger and Spalding (1939) found *Trichinella* larvae in the venous blood of 3 of 6 children. The intradermal tests were negative in all. Precipitation tests were positive in 2, but negative in 1. Dammin (1941) reports one case in which larvae of *Trichinella spiralis* was found in the arterial blood after unsuccessful examination of the venous and capillary blood. In this case the initial skin reaction to the National Institute of Health *Trichina* antigen 1:10,000 was of the delayed, positive type. This was followed by 2 negative reactions.

It is unfortunate that the skin tests do not give positive reactions in trichinosis as early in the disease as is desirable. According to McCoy and his associates, they may

be positive with certain dilutions in 11 days, or according to Spink and Augustine (1935) in 14 days. It has been reported that the tests may remain positive for over 7 years after clinical recovery. Also, it has been found by McCoy, Miller and Friedlander that in a series of 124 cases in rural Louisiana heavily infected with other nematodes (chiefly *Trichuris*) but probably free from *Trichinella*, 62 per cent gave positive reactions, presumably group reactions. Thus while the test promises to be of considerable practical value, a positive result is not conclusive, particularly if other parasites are present. A positive *precipitin reaction* has also been employed but appears too late in the disease to be of practical diagnostic value. It usually does not become positive until the end of the fourth week after infection and it may remain positive for a year after the infection. Bachman and his associates (1934) report various conditions which give nonspecific and anomalous reactions.

Treatment.—The treatment employed can only be symptomatic and of a general nature, for no specific remedy for *trichiniasis* is known. The adult parasites in the intestine are difficult to dislodge since they may bore deeply into the intestinal walls. Nevertheless when gastro-intestinal symptoms follow the eating of pork which was not well cooked, an attempt may be made to dislodge them by evacuating thoroughly the gastro-intestinal-tract. Castor oil may be given at once and followed shortly afterwards by magnesium sulphate. Chandler suggests that tetrachlorethylene or gentian violet should be tried to dislodge the parasites. Often, however, the infection is not recognized until the larvae are migrating through the body. This is the most critical stage of the disease, and if the patient can survive the toxic products of what may sometimes be millions of migrating and developing parasites until they reach full size and become encysted, the critical stage is usually over.

Beard and DeEds have reported some success in reducing the number of larvae in the muscles of experimental rats by administering sulfanilamide* and sulfathiazine. Someren (1939) reports that he was able to reduce the number of adult parasites in the intestinal wall by feeding butolan (Bayer).

Wantland (1934) has shown experimentally that calcification of well-formed cysts can be hastened by administration of calcium and ergosterol. Von Brandt (1938) has found that such calcification can be hastened even more by large doses of parathormone. However Perez points out that this is not wise in man as calcium deposits form before any effect on larvae is noted.

Prevention.—Personal preventive measures against trichinosis are simple and consist in abstinence from all pork which is not thoroughly cooked. Numerous experiments show that trichinae are killed usually when the temperature reaches 55°C. (Ransom and Schwartz). More recently, Otto and Abrams (1939) found in their experiments that a few trichinae apparently tolerated 55°C. for 1–5 minutes and that 7 out of 1000 in one experiment apparently tolerated 60°C. for 5 minutes. They regard these slight discrepancies as the result of the differences used in exposing larvae to the infected temperature.

Ransom and Schwartz pointed out that the larvae are quickly destroyed by exposure to a temperature of 55°C. gradually attained: 55°C. is the minimum temperature which quickly kills practically all larvae. The Federal Government requirement of 137°F. (58.3°C.) in the heat processing of pork offers an adequate margin of safety.

* Andes et al (1941) who administered this drug to 8 persons in whom the diagnosis had been made within 3 days of the onset of symptoms, reported complete and immediate recovery.

It should be emphasized, however, that pork must be cooked for a length of time proportionate to its weight in order to insure the permeation of heat to the center. Experiments have shown that at least 30–36 minutes boiling should be allowed to each kilogram of weight (2¼ lbs.). Hurried roasting does not destroy the parasites as long as red or raw portions are left in the center.

Salting and smoking of pork are not efficacious unless carried out with great care.

Augustine (1933) has shown that quick cooling to −34°C., or quick cooling to −18°C. followed by storage at that temperature for 24 hours, or at −15°C. for 48 hours, renders the trichinae non-infective. Cold storage for 20 days at a temperature of −15°C. is required by the United States Bureau of Animal Industry for pork products to be used uncooked.

Public Health.—Trichinosis constitutes one of the major public health problems of today. Its high incidence in the United States and a number of other countries indicates that little has been accomplished by propaganda against eating uncooked pork, or in the special treatment of pork which is to be eaten uncooked, in Government-inspected slaughter houses. While the inspection of pork formerly performed in the larger slaughter houses undoubtedly reduced the amount of the disease, Stiles has emphasized that such examinations are not entirely dependable and set up a false sense of security. Moreover, the most dangerous source of infection is pork butchered on farms and in small local establishments which are not inspected. A number of epidemics have been traced to such pork from country slaughter houses.

A very dangerous and wide-spread custom which leads to the dissemination of the disease is that of feeding raw garbage to hogs. Nearly 40 per cent of the cities of the United States of over 4500 population and 50 per cent of the cities of over 15,000 dispose of garbage by feeding it to hogs. The rate of infection is highest on the North Atlantic Coast and in California, where hogs are most extensively fed on garbage. In the Middle West, where hogs are raised on pastures and fed on grain, the incidence is lower, and it is still lower in the South, where hogs are generally allowed to roam the fields and woods and do not have easy access to kitchen scraps or city garbage.

McNaught and Zapater (1941) believe that rodent control is a statistically verifiable method of reducing trichinosis percentage in garbage-fed swine.

Hall (1937) has found that garbage fed swine have trichinae between 3 and 5 times as frequently as do grain-fed swine and hence are especially important as a source of human trichinosis. Trichinosis in swine is apparently traceable to the eating of uncooked pork scrappings in garbage, table scraps, swill, and similar substances much more often than it is traceable to the eating of rats by swine. Nevertheless, a small amount of trichinosis in swine occurs from their eating infected rats and the disease is transmitted from rat to rat by cannibalism.

In view of these facts, it is exceedingly desirable in places where it is believed to be economically necessary to feed garbage to hogs that it should be cooked with steam or boiling water. The city health departments should not only prohibit the feeding of uncooked city garbage on municipal hog farms but should also prohibit its sale to private contractors.

The destruction of rats and keeping of dead rats from hogs is also desirable. It obviously is important that all the carcasses and viscera of hogs dying on farms should be carefully destroyed, preferably by cremation.

Nelson (1939) suggests as an additional measure of protection that skin tests on all hogs should be permitted and that in those giving positive reactions the meat should then be especially refrigerated before use. In a series of 211 hogs tested by this method, in 97 per cent the results coincided with those obtained from microscopical examination of digested diaphragms. Whether this method is a practicable one and thoroughly reliable is not yet known.

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In the intestine, the parasites develop a mouth capsule and become attached to the intestinal wall. After becoming sexually mature and mating, oviposition takes place.

It was recognized that the disease was very prevalent in the southern United States as long ago as 1849, as is shown by the writings, among others, of Duncan, who noted the frequency of anaemia, often associated with dirt eating, among the slaves. He also described the oedematous legs, the protuberant belly, and cardiac palpitation. Stiles emphasized that the disease was probably of frequent occurrence in the southern United States, and after a study of material sent him by Smith and Claytor in the United States, and later by Ashford in Puerto Rico, he, in 1902, recognized that the species of hookworm common in this country was a new one. He first described and named it *Uncinaria americana*, but as the genus *Uncinaria* had been preempted for the hookworm of the fox, as above mentioned, it was not valid for this new species and the name was later changed to *Ancylostoma americanum* and finally to *Necator americanus*.

Geographical Distribution.—Hookworm disease is widely diffused and may be said to occur in practically all tropical and subtropical countries. It, however, is usually rare in temperate or northern countries, except in mines or tunnels, where sanitation is poor and suitable conditions of warmth and moisture exist. Thus it has been found by Haldane to be the cause of severe anaemia in a Cornish mine and in parts of Belgium. It is more common in the south of Europe. It is extremely prevalent in India and Egypt, as well as in China and other parts of the Far East. It is a very important infection in Puerto Rico and is common in the Philippine Islands. It is extensively distributed in South America, especially Brazil, as well as in Central America, the

Country		Author
Africa:		
Egypt....................	69	O'Connor
Rural population, Egypt	50–90	Scott
Victoria Nyanza..........	49.5	N. P. Jewell
Uganda..................	91.1	H. L. Duke
Brazil:		
Amazona................	95.2	DaMatta
Colombia................	48–88	Henao & Toro Villa
Panama..................	80.4	Rockefeller Com.
Mexico..................	80.	Moillet & Careno
West Indies:		
Cuba....................	51	Spear
Honduras...............	79.2	N. Barlow
Puerto Rico.............	75	Rockefeller Com.
Granada................	64.2	R. P. Cockin.
Japan:		
Loochoo................	84.3	Hoki
Philippines..............	52	Garrison
Borneo..................	59	Christe & Ledingham
Samoa...................	85.1	O'Connor
East Indian Islands.........	83	
New Guinea.............	75.3	N. Clapier
Indo-China..............	39–62	Mathis & Leger
Siam du Nord............	94.3	W. F. Kerr
Assam..................	93.6	A. C. Chandler
Ceylon..................	95	Chopra

Islands of the Carribean, Mexico, and the southern states of the United States. The inhabitants of many of the islands of the Pacific are heavily infested. It also occurs on the north coast of Africa, central and south Africa, and in Australia.

The table as shown on p. 1252 illustrates the rate of infection found in approximately 50 per cent or over in a number of surveys, usually following simple microscopical examination of the stools. No doubt, high rates might also be found in surveys performed in a number of other moist, tropical regions. In the United States, for example, Smillie (1924) in Alabama, found 100 per cent of those examined infected, and Manson-Bahr, 1940, says in some districts in Jamaica the whole population is infected.

Chandler (1929) and Faust (1940) have referred in detail to the different geographical distribution and prevalence in some countries of the 2 species, *Ancylostoma duodenale* and *Necator americanus*. However, often both species are found in the same country. The latter parasite has been an important agent in the production of the "tropical anaemia" of Puerto Rico and in the production of "laziness" in the poor white population of the southern U. S. and in the natives of certain sections of the Philippine Islands.

In the United States, Keller, Leathers and Densen (1940) point out that the rate of infection of hook-worm in 6 of 8 of the Southern States was 36.6 per cent from 1910–14 and 11.2 per cent from 1930–38. In the latter period, the states in the order of prevalence of the disease from highest to lowest were as follows: Mississippi, South Carolina, Alabama, North Carolina, Kentucky, and Tennessee.

Zoology

The hookworms are classified in the *Superfamily* **Strongyloidea.**

In this superfamily the male has a caudal bursa, a prehensile sort of expansion at the posterior end for copulatory purposes.

The mouth is usually provided with six papillae and at times with a chitinous armature. The oesophagus of the adult is without posterior globular bulb but may be greatly swollen.

Families discussed: Ancylostomatidae; in which there is a well developed caudal bursa and buccal capsule, aperture of buccal capsule guarded by cutting plates or teeth. Strongylidae; with well developed caudal bursa and buccal capsule, aperture of latter guarded by a corona radiata. Trichostrongylidae; having a well developed caudal bursa, buccal capsule when present rudimentary. Metastrongylidae; with a poorly developed caudal bursa having atypical rays and buccal capsule absent or poorly developed. The human hookworms belong to the family ANCYLOSTOMATIDAE.

The oval cutting organs in the species of the genus *Ancylostoma* consist of tooth-like processes, while in the genus *Necator* they consist of semilunar plates.

Significance.—The hookworm infections of man are nearly all due to two species; *Ancylostoma duodenale*, the "Old World species," and *Necator americanus*, the "New World species." In fact both are widely distributed throughout tropical and subtropical regions and are found in temperate regions in mines, tunnels or other localities in which they find warmth and moisture. The adult worms are found in the small intestine (jejunum) of man, sometimes in enormous numbers (1500 or more). They attach themselves to the mucosa from which they suck blood and cause some free bleeding. As a result of this blood loss, perhaps of secondary bacterial infection and possibly also by the secretion of a toxin, they may give rise to a severe (hypochromic) anaemia, weakness, general debility and chronic ill health, with retardation of development of infected children. Very severe infections may be quickly fatal. Many cases, however, are practically symptomless. Newcomers into an endemic area usually suffer more severely than the native population which has acquired some immunity to the parasite or to its effects. Recent studies have shown the great importance of a deficient diet in the production of the anaemia, which can sometimes be relieved by the administration of large doses of iron without elimination of the parasites. The use of anthelmintics, however, is important, especially in connection with ultimate cure. The hookworm constitutes a major public health problem in many infested regions. In some localities, over 90 per cent of the population are infected.

The eggs, which are passed in the faeces, are not infective for man. They hatch in soil and water, later, after moulting, developing into filariform larvae, which constitute the infective stage for man.

Ancylostoma duodenale (Dubini, 1843), originally an "Old World" species, has spread over large parts of Africa (especially Egypt) and Asia. It occurs in limited areas in North and South America. It also has been found in the gorilla, tiger, civet cat, and has been experimentally developed in young dogs and cats (Blacklock, 1938).

The male is about 10 mm. long and 0.4 to 0.5 mm. wide, the female about 12 by 0.6 mm. The sexes are easily differentiated by the shape of the tail, pointed in the female, broadened in the male into an umbrella-like expansion, the copulatory bursa. The large oval mouth has *four claw-like teeth* on the ventral side of the buccal cavity and 2 knob-like teeth on the dorsal aspect. It also has a pair of ventral lancets below the 4 ventral teeth. The anterior part of the body is filled by the oesophageal gland which secretes a substance inhibiting coagulation which is discharged through a dorso-median cone. The anterior end of the body is bent rather sharply in the same direction as the general body curve. In the female the vulva is located in the posterior half of the ventral surface. The copulatory bursa of the male shows a shallow cleft between the main divisions of the dorsal ray, which has tridigitate terminations. There are two distinct hair-like copulatory spicules. During copulation the worms join so as to form a Y shaped figure.

The females after fertilization give off great numbers of ova, variously estimated at 6000 to 20,000 or more per day for each worm. The ova measure about 40 by 60μ. They have a thin shell, a wide clear glassy outer zone and a granular central zone which (in freshly passed faeces) is usually divided into 2 to 4 (never more than 8) cells.

Necator americanus (Stiles, 1902), the "New World species," although first discovered in the United States appears to have been native in Africa and was probably brought to America by negro slaves. It has also been found in the pygmies of the Eastern Congo and in Rhodesia. It is wide spread in Northern South America, the West Indies, in India, Ceylon, the Malay peninsula, the Philippines and the Pacific Islands. It has been reported in the pig and from several species of monkeys. It differs from Ancylostoma duodenale in the following points:

It is slightly smaller, the male measuring 8 by 0.3 mm., the female, 10 by 0.4 mm. The buccal cavity is smaller, round, and is equipped with 2 prominent ventral chitinous plates and 2 rudimentary dorsal plates in place of the teeth. The median dorsal cone projects conspicuously into the buccal cavity. Deeper in the cavity are one pair each of dorsal and ventral lancets, or pharyngeal teeth. The anterior tip of the body is bent back sharply in a direction opposite to that of the general body curve.

The vulva is in the anterior half of the body. The caudal bursa is deeply cleft, and the terminal portions of the dorsal ray are bipartite instead of tripartite. The spicules are fused at their tip and end in a single barb. The ova are slightly larger (40 by 70μ).

The *life history* is practically the same in both species. Segmentation of the ova does not progress within the intestine, probably because of lack of oxygen. After being passed, in the presence of warmth (14° to 37°, preferably 27°C.), moisture (muddy water, damp earth) and oxygen, segmentation progresses rapidly so that within two days a small *rhabditiform larva* is hatched. (For differentiation, see p. 1280 and Fig. 279.) This feeds voraciously and grows rapidly, reaching a length of 0.3 mm. on the third day, when it moults; and 0.55 mm. on the fifth day, when it moults again, loses the bulb-like swellings of the oesophagus and is converted into a *filariform larva*, the infective stage. The old cuticle is not shed but is retained as a protecting sheath. The parasite then enters into a resting stage in which it ceases to take food, although it remains actively

motile and can crawl up blades of grass or up the vertical sides of mines. Cort found, however, that they do not migrate more than 4 inches from the place of development. Before becoming ensheathed hookworm larvae are readily destroyed by direct sunlight, by chemicals, or even by dilution of the faeces, and especially by the urine. After ensheathment they become relatively resistant and in shaded moist ground may live 4–8 weeks in the tropics (even though they lose their sheath), although according to Cort not longer than this as some have maintained. In a cool, moist environment they may live much longer. They are still quite sensitive to desiccation and to extremes of temperature.

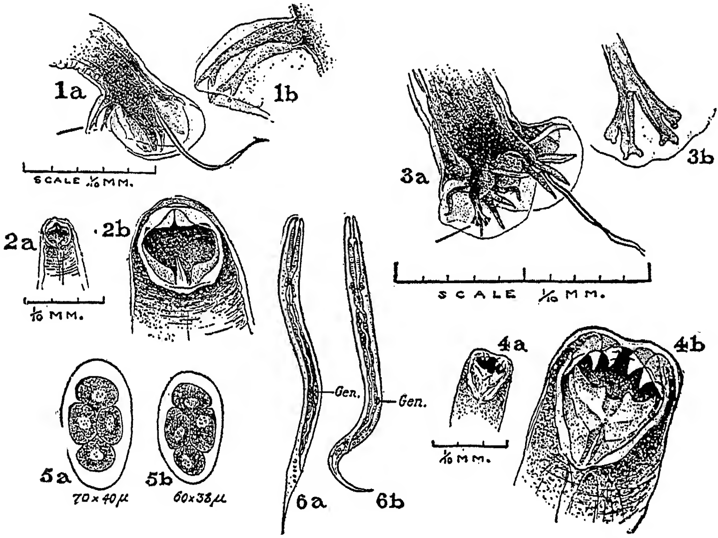

FIG. 279.—1a, Copulatory bursa of *Necator americanus*, showing the deep cleft dividing the branches of the dorsal ray and the bipartite tips of the branches; also showing the fusion of the spicules to terminate in a single barb. Scale 1/10 mm. 1b, Branches of dorsal ray magnified. 2a, The buccal capsule of *N. americanus*. 2b, The same magnified. 3a, Copulatory bursa of *Ancylostoma duodenale*, showing shallow clefts between branches of the dorsal ray and the tridigitate terminations. Spicules hair-like. 3b, The dorsal ray magnified. 4a, The buccal capsule of *A. duodenale*, showing the much larger mouth opening and the prominent hook-like ventral teeth. 4b, The same magnified. 5a, Egg of *N. americanus*. 5b, Egg of *A. duodenale*. 6a, Rhabditiform larva of *Strongyloides* as seen in fresh faeces. 6b, Rhabditiform larva of hookworm in faeces eight to twelve hours after passage of stool.

If infected soil comes into contact with the skin, stimulated probably by the warmth, the larvae become very active and *burrow through the skin*, causing the familiar symptoms of "ground itch." Apparently any part of the skin can be penetrated, and only a few minutes are required for the process. The interdigital spaces of the feet are common points of entrance. In the subcutaneous tissue they enter the veins or lymphatics and are carried passively to the lungs. Here they penetrate the walls of the capillaries and alveoli into the air sacs and proceed or are carried up the bronchi and trachea to the pharynx. They are then swallowed and reach the intestine about one week after infection, having undergone a third moulting. The larvae grow rapidly, undergo a fourth moulting after another week (when they measure about 2 mm. by 0.13 mm.), and reach maturity about a month after entering the body. Sai Ryo (1937) who placed 300 *Ancylostoma* larvae on the skin of 3 volunteers, found eggs in their faeces

on the 54th, 55th and 57th days. He thought that in such instances between 290 and 295 of the larvae penetrated the skin. By treatment, he recovered adult worms numbering 77, 78, and 83 respectively from their faeces.

The exact duration of life of the adult parasites is not precisely known, but probably varies from a few months to 6 years. Infection can also occur if the larvae are swallowed. Fulleborn showed that in experimentally infected animals a few larvae can reach the intestine without passing through the lungs.

The number of parasites which must be present to produce disease is variously estimated and doubtless varies greatly. As a rule, it is said it probably requires 500 worms several months to cause severe symptoms. However, much depends upon the resistance of the patient. In some cases it is believed that 25 worms, or even fewer, may cause definite disturbances. There is frequently not a close parallelism between the number of worms and the severity of symptoms, though Darling suggested the reduction in the haemoglobin seemed proportionate to the number of worms present.

FIG. 280.—Ovum of *Ancylostoma duodenale*. (After J. A. Thomson.)

Epidemiology.—When faeces containing hookworm eggs are deposited where conditions of moisture, warmth and shade exist, they develop into the infective stage, a filariform larva which is the non-feeding but motile larva inside the cuticle formed by the second moulting. While eggs and younger larvae are killed rapidly, the encysted larvae withstand partial drying for considerable periods.

Stiles noted that the more favorable conditions for development are in a porous sandy soil, rather than in a clay one. Where a sewerage system exists, there is very little danger of the spread of hookworm disease and the same is true where there is proper disposal of the faeces by burning, boiling, or treatment in a septic tank. In rural districts, however, where the stool is often deposited in the shade and retirement of a clump of trees, the soil becomes infested with myriads of larvae, so that one standing subsequently with bare feet on such a spot easily becomes infected. It is for this reason that shoes are of protective value. Infection can also occur if the larvae are swallowed. In infected mines with temperatures below 22°C. infection is rare (6 per cent); from 22°C. to 25°C. more common (16.6 per cent), and above 25°C., it may reach high figures (61 per cent).

The negro race does not suffer from the infection as does the white. The former appear to have an immunity, but often serve as carriers of the disease. Keller, Leathers and Densen have made a comparison of the incidence of hookworm infection in 17,458 negroes and 59,028 white persons in the same counties in the southern United States during 1930–1938. The incidence in negroes was about one-fourth that in white individuals, and the average intensity of infestation was about one-half that found in white persons.

There is a difference of opinion as to the length of time the parasites may live in man in the absence of reinfection. Some consider this period one of a few months, others of 2 or 3 years. It has been considered that a case leaving an infested region will get rid of his parasites within 7 years.

Nowhere in the world has the study of hookworm infection been pursued so intensively and carefully as in parts of the southern United States. This work was begun on a large scale by the Rockefeller Sanitary Commission in October 1909, with Dr. C. W. Stiles of the U. S. Public Health Service as Scientific Director.

Among the specific objectives of the Commission was to make an infection survey with an active and reliable estimate of the degree of infection by counties; to make a sanitary survey which should show by counties the condition of soil pollution responsible for the presence and spread of the infection; to demonstrate to the people that hookworm disease was a serious handicap; that it was curable and preventable; to help the practicing physicians of the state in diagnosing the disease and controlling it; to make definite, measurable reduction in the degree of infection for the heavily infected areas; to make definite, measurable increase in the sanitary index of these areas; and, if possible, to help lay the foundation of a state and local health service that should in the end take care of hookworm infection and other preventable diseases.

Keller, Leathers and Densen (1940) have summarized the success of this work in 8 of the southern states during the periods 1910–14 and 1930–38. They report that in the early period 577,590 specimens of faeces were examined, and in the later period 424,511. The numbers found positive in the early and later periods were 240,895 and 81,913 respectively.

After adjustment for the distribution of the population, the percentage found positive in 6 of the 8 states was 36.6 per cent in the earlier period and 11.2 per cent in the later period, resulting in a very striking reduction.

While there is still a widespread distribution of hookworm, the areas of highest incidence are confined to the coastal plain and sandy soil areas of each state.

The age distribution shows that the greatest prevalence was in the group 5–19 years of age. The peak of incidence, 24.5 per cent, was reached in the age period 15–19. In the preschool children and adults, the incidence was about one-half as great as that found in the school age group.

Scott (1937) in the study in Egypt of the data from 2,000,000 hospital cases and from nearly 40,000 persons examined in their houses, found that males and females acquired infection at about the same rate up to the age of 10. In females, the maximum is reached at 20 years, and in the male at 15 years. The males are always more heavily infected. The acquisition of the infection was markedly associated with field work. In Egypt, the intensity of infection as shown by egg counts is everywhere very low as compared with most countries. Scott believes this to be due to the low soil infestation intensity.

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Chapter XLIV

ANCYLOSTOMIASIS

and Other Intestinal Infestations with Related Nematodes.

Definition.—Infection with the hookworms of the family *Ancylostomatidae*.

History and Geographical Distribution

History.—It is very probable that hookworm disease existed in Egypt in the remote past and it has been claimed that a disease mentioned in the Ebers Papyrus was of that nature. It was also mentioned by Avicenna, the Persian physician (980–1037 A.D.).

Froelich, in 1789, found hookworms in the fox and named them hookworms from the hook-like ribs of the copulatory bursa. He proposed for this parasite the generic name of *Uncinaria*. Hence, since the genus *Uncinaria* was preempted for the hookworm of the fox, it was not valid for the human species subsequently described. The first accurate description of the human parasite was given by Dubini from material obtained at an autopsy. In 1838, he noted that these worms were generally found in very anaemic cases and that the mucosa of the duodenum or jejunum where the parasites were found, frequently showed punctate haemorrhages. On account of the 4 ventral teeth projecting from the mouth of the nematode, he gave it the name *Agchylostoma*, or more correctly *Ancylostoma* (ἀγχύλος, hook, and στόμα, mouth).

Bilharz (1853) and Griesinger (1854) regarded the parasite as probably being responsible for a severe form of chlorosis very common in Egypt. In 1866, Wucherer connected hookworms with a disease in Brazil called *opilacão*. In 1878, Grassi and Parona, noted that the disease could be diagnosed by the finding of the characteristic eggs in the stools of patients.

Perroncito, in 1879, made the important discovery that the severe and fatal anaemia which was prevalent among the workmen employed in the construction of the St. Gothard tunnel was due to hookworm infection. It was especially through this demonstration that the importance of the parasite as a pathogenic organism became recognized.

About the same time, it became generally considered that the anaemias which affected workmen in a number of mines were of a similar nature. Perroncito (1880) reported the development of the free-living, first stage larvae hatched from eggs and their metamorphosis into filariform larvae, while Leichtenstern, 1887, found that mature filariform larvae when introduced by the mouth into the intestinal tract develop into adult parasites in the small intestine.

Löoss (1897), in Egypt, first accidentally infected himself by placing filariform larvae upon his skin and later, by experimental studies on the dog with *Ancylostoma caninum*, he demonstrated the complete route of migration and the stages of development of the parasite from the time of its cutaneous invasion and passage through the lungs up the respiratory tract, over the epiglottis, and thence downward into the small intestine.

Whether the eosinophilia is an evidence of a production of a toxin is not clear. However, the eosinophilia may be due to the irritation of the passage through or presence of the larval forms of the parasite in the skin. Nevertheless there is still some difference of opinion about the production and effect of a toxin in regard to the anaemia.

In addition, faulty diet has been pointed out as one of the chief causes of the anaemia. DeLangen, 1936, has particularly emphasized that diet and general hygiene have important contributary effect on the development of the severe anaemias. Diet poor in protein and lipoid substances (which are essential for red cell regeneration when extra vascular blood loss is continuous) obviously may influence the anaemia, especially if there is deficiency in the gastric juice. Stewart has emphasized that heavy nematode infections lessen protein digestion. Apparently such poorly nourished individuals are also less resistant to infection. Another factor, individual resistance, is important. Manson-Bahr (1940) points out that many inhabitants of tropical countries are in a state of chronic starvation, living on coarse, bulky unnutritious food and are prone to dilatation of the stomach and dyspeptic troubles. In such individuals any additional cause of malnutrition, as the presence of a very large number of *ancylostomes* and a daily, though perhaps small, loss of blood, may be sufficient to turn the scales against them.

Castle, Rhodes, Payne and Lamson (1934), in a study of 83 patients with hookworm anaemia in Puerto Rico, thought the anaemia was due mainly to insufficient blood production as a result of a deficiency of available iron and other haematopoetic substances in the body. This deficiency was postulated to be produced by multiple factors, defective diets, or indirectly by gastro-intestinal changes, or by blood loss due to the hookworm. Various combinations of these factors were probably involved in different patients. No effect of the presence of the hookworm could be demonstrated other than could be accounted for by its ability to remove blood from the patient. The removal of the hookworm was shown to produce slight clinical improvement and to have considerable effect upon red blood cell production, but to have little effect upon haemoglobin production, within several weeks. The daily administration of 6 grams of ferric ammonium citrate with or sometimes even without removal of the parasites was attended by striking improvement of the blood values of the clinical conditions of the patients.

It seems clear then that in many cases of hookworm infection when iron and liver are added to the diet the anaemia may be greatly reduced. Scott (1938) points out that it is not the number of hookworms that determines the onset and degree of hookworm anaemia so much as the host's iron reserve.

Character of the Anaemia.—The anaemia is often the most prominent symptom in hookworm infection and is generally recognized first by the pallor of the mucous membrane. It is accompanied by the usual symptoms of weakness, fatigue, palpitation and dyspnoea. The children are often physically and mentally backward—puberty may be delayed. Often the abdomen is distended and rapidly developing asthenia may occur. Ashford and Panyes (1933) noted gross intestinal haemorrhage in several cases. The anaemia may reach the most severe stages quickly, but in other instances slowly. It has usually appeared by 10–20 weeks after infection. Eventually a severe grade of secondary anaemia usually results. The anaemia is hypochromic and usually microcytic in character. The haemoglobin content falls first, and later the number of red blood corpuscles. The color index is always less than 1 in severe cases.

Fikri and Ghalioungui found that the average total blood volume in cases of ancylostomiasis was 79.5 cc. per kg. body weight. However, the average plasma volume in ancylostoma anaemia was 62.6 per kg., so that the diminution of the total blood volume could be accounted for entirely by the diminution of the red blood corpuscles.

Villela (1937) found low values for plasma proteins in some cases. The average red blood cell count varies greatly. Suarez (1933) in the study of 19 cases, found from 1,000,000 to 3,500,000. Biggam and Ghalioungui give 2,900,000 as an average count, with a haemoglobin of 27.8 (Sahli) in 100 cases in which the average diameter of red blood corpuscles was 7.44. The reticulocytes were always less than 1 per cent. However, Sai Ryo found them increased after the third week. Landsberg (1937) found that in severe hookworm anaemia of dogs, which later was fatal, there was a marked reticulocytosis. Eosinophilia is usual, and may reach even as high as 90 per cent. Suarez (1933) found the eosinophiles varied from 2–15 per cent.

Lichtenstein (1936) found

Haemoglobin, Per Cent	Average Percentage of Eosinophiles
Between 70 and 60	32
Between 60 and 50	23
Between 50 and 50	10
Between 40 and 30	11
Between 30 and 20	2.5
Below 10	0

From these studies it would appear that the more severe the anaemia the smaller number of eosinophiles, and that in very severe cases they may even disappear entirely. Whitby says the eosinophilia may take 3 to 4 weeks to develop. Sai Ryo (1937) in his 3 experimental volunteers, found eosinophilia present the third day after the infection, and it reached its maximum height in the sixth and seventh week and decreased after the fifteenth week. In these three volunteers, 300 filariform larvae were placed upon the skin. The number of worms which penetrated was 295, 292, and 291. The number of adult worms recovered in the faeces from these cases was 83, 78, and 77.

In regard to the leucocytes, Suarez reported counts of from 2500 to 10,000 per cu. mm. there may be a general fall in their total number later, but there are no other peculiarities in the leucocyte count.

Gastric Secretion.—The gastric secretion has varied. Rhoads and Castle (1932) state "achlohydria is common." On the other hand, Biggam, 1934, rarely found any deficiency of free hydrochloric acid.

Opinions vary with reference to the presence of blood in the faeces, according to the different methods employed for its detection. When not obvious, occult blood is usually demonstrable.

Symptomatology

In a secondary anaemia, with early and marked cardiac palpitation together with epigastric tenderness and a tendency to mental retardation and physical deterioration, one should always examine the stools for hookworm eggs. The course of the disease is often decidedly insidious and indefinite, and the clinical diagnosis notoriously uncertain, as shown by many reports where physicians of experience, after examining a number of persons in a mill or school and diagnosing only 2 or 3 per cent as showing physical signs of the disease, have been astonished, upon examination of the faeces of the group, to obtain positive evidence of infection in 70 to 80 per cent of the number examined.

For convenience, it is well to divide hookworm cases into 3 groups; (1) where the infected person fails to show any special evidence of abnormality, the diagnosis resting almost entirely on the finding of ova in the faeces. Such patients may show very slight reduction in haemoglobin and only admit of a certain lack of energy. The best indication that hookworm infection is doing the host injury is that after treatment

the individual gains in weight and energy and shows improvement in mental acuity. (2) Mild cases with moderate degrees of anaemia, the haemoglobin percentage ranging from 55 to 75 per cent. In these cases there is rather marked epigastric tenderness with frequent attacks of acid eructations. Cardiac palpitation and a tendency to shortness of breath may be quite noticeable. Headache and vertigo may be present. (3) Severe cases. In such cases we may find extreme anaemia with haemoglobin percentages around 35, or even as low as 15. These cases usually are very weak and show marked cardiac palpitation and dyspnoea upon the slightest exertion. There is often dilatation of the stomach and a protuberant abdomen. The red cells may fall below 1,000,000. There is also oedema, especially about the feet and ankles. Tinnitus aurium is rather frequent. Such cases often show depravity of appetite, the best-

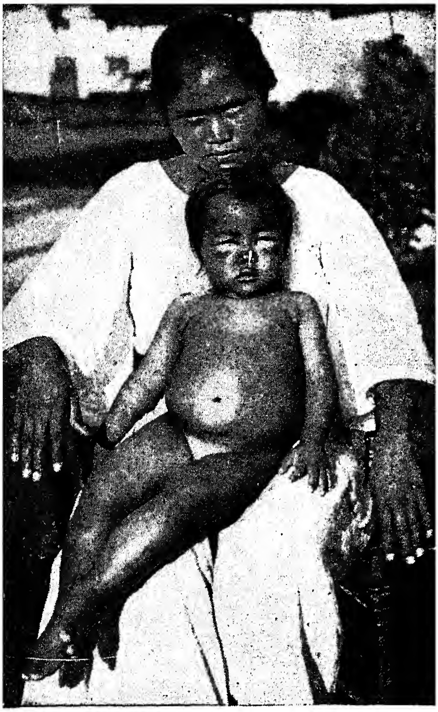

FIG. 283.—Fatal case of ancylostomiasis. Red cells 810,000. Hb. 15%. White count 6400. Eosinophiles absent. Upper part of small intestines lined with hookworms. (From U. S. Naval Medical Bulletin.)

known craving being that for earth. ("Pica," or geophagy.) Other patients crave chalk, wood, cotton, etc.

As regards the suggestions of Smillie and Augustine to classify hookworm cases as "carriers" where the number of worms harbored did not exceed 100 and as "patients" when the adult worms exceeded 100, Stiles recognized that such a computation, based on egg counts, may measure objective symptoms but that it will not bring under treatment cases where the subjective symptoms are important. Under the above grouping, it was recommended that carriers need not be treated. Keller, Leathers and Densen (1940), in their studies of hookworm infection in the southern United States, found that about one-fourth of the individuals had moderate, heavy or very heavy worm infestation, sufficiently severe to produce clinical symptoms. The remainder of the cases were classified as very light infestations.

It is in children that the most serious effects of the disease often occur, there being marked stunting of the growth with a corresponding mental backwardness. Such children may show marked retardation and delay in answering the question asked them and often repeat it in a drawling manner. Tested by the Binet-Simon method, one may find a 16 year old child to have the mental development of a 10 year old one, and, at the same time, one may note that from a standpoint of physical development the child only seems 10 years old. As the child approaches adult age, a striking lack of sexual development and the lack of pubic hair may be observed. In girls there is delay in the onset of the menstrual periods, or these may never appear.

The disease often exerts a deleterious influence on pregnancy and in badly infected districts it has been reported as a common cause of repeated abortions and miscarriages. In pregnant women, if the haemoglobin percentage has fallen below 60, unless treatment is prompt death often occurs. Impaired renal function has been an outstanding feature in the majority of pregnant women suffering from ancylostomiasis. Manson-Bahr points out that heavily infected cases show a predisposition to develop the toxaemias of pregnancy, such as preeclampsia, eclampsia and nephritic toxaemia.

In hookworm infection, as a rule, the temperature is normal throughout the course of an uncomplicated case, though occasionally low fever has been noted and in the later stages the temperature may be subnormal. During the first week or so following a heavy infection, there may be pulmonary manifestations when the larvae are migrating by way of the lungs.

In the diagnosis of a case, Stiles attached much importance to a tallow-yellow color of the alae of the nose and forehead, as well as to the eye characteristics, which were said to resemble the eye of a fish, or that of an intoxicated person. He also noted that the pupil tends to dilate instead of to contract when the patient looks at a bright light. Stitt (1929) thought that the condition might be rather one of hippus. Dimness of sight is frequently noted and in severe cases opthalmoscopic examination may reveal retinal haemorrhages. There may be night blindness. Ascites may be present in advanced cases.

Dermatitis.—In from 80–90 per cent of cases there is a history of dermatitis, particularly of toes or feet, which has been commonly called "ground itch," "foot itch," or "dew itch." This is most frequent between the toes, or on the inner side of the sole of the foot. The irritation is due to the penetration into the cutaneous tissues of the hookworm larvae. The itching is intense and secondary infections often occur as the result of scratching. Vesicles appear about the second day and are often ruptured by the scratching, with a resulting pustular or impetiginous condition.

The skin and hair are generally dry. The evidence of brown patches in hookworm infection is apparently much more common on exposure to *Necator americanus* than *Ancylostoma duodenale*, and with the latter parasite they are not often encountered. A form of "creeping" eruption due to exposure of the skin to filariform larvae of *Ancylostoma braziliense* has been reported as occurring particularly along the southern United States coast. Kirby-Smith and his associates, 1917–1927, have especially studied this infection. In the course of 2 or 3 days after the skin has been exposed to soil containing the larvae, reddish itchy papules appear at the site of the infection. The larvae by their movements gradually produce serpiginous tunnels in the stratum germinitivum. The lesion is at first erythematous but soon becomes elevated and vesicular. The parasites move onward at the rate of several millimeters to a few centimeters per day and abandon a part of the tunnels they have produced, these becoming dry and crusty. The move-

ments of the larvae and the tissue irritation give rise to an intense pruritis, with scratching and often subsequent pyogenic infection. Round cell infiltration and accumulation of eosinophiles may occur around the tunnels. The parasites may continue their activities for several weeks or even months, but very rarely invade the circulation. The lesions are most frequently on the feet and hands. White and Dove and Maplestone (1933) have also studied the creeping eruption, the latter having observed it in coolies in India. Apparently these species of hookworm do not find appropriate physiological conditions in human beings for the continuation and deeper invasion of the tissues. The infecting parasite has sometimes been referred to as *larva migrans*.

Other forms of creeping eruption are referred to in the chapter on Diptera.

Symptoms in Detail

Skin Manifestations.—The dermatitis following the penetration of the larvae occurs most often about the toes or inner side of the sole of the foot. Ashford found in a study of 19,000 hookworm cases in Puerto Rico that 96 per cent gave a history of initial dermatitis. On the other hand, in Egypt where ancylostomiasis is prevalent ancylostome dermatitis is not observed. Subsequently, during the migration and development of the parasites in the body, an urticarial rash may occur. The skin is often very dry and often a pale, earthy color. A tallow-yellow tinting of the alae of the nose may be observed. The hair is dry and scanty, or absent in pubic and beard regions. Oedema, especially of ankles or feet, is common.

Circulatory and Respiratory Systems.—Palpitation of the heart is early and marked. Functional murmurs are frequent in the advanced stages. Pulsation of the neck veins is also common. The pulse rate averages about 110 and the blood pressure is low. There is frequently some dilatation of the heart to the right. A high pulse pressure is common in severe cases. Shortness of breath on slight exertion is the most common respiratory symptom. There are at times cough and bronchitis, probably sometimes induced by the irritation of the larvae in the pulmonary alveoli during the course of migration.

Digestive System.—Epigastric tenderness is very characteristic. The pain has sometimes suggested duodenal ulcer.* The stomach is often dilated and the gastric juice may be hyperacid. It has been suggested that the desire to neutralize this acidity with an alkali is the explanation of the desire for alkali-containing earth on the part of "dirt eaters." As the anaemia increases the acidity often diminishes and achlohydria may occur. Patients often are pot-bellied. Constipation is rather a common feature, though diarrhoea may occur. The stools may very rarely show macroscopic blood. In a few instances, bloody mucus has been reported.

Nervous System.—Hookworm patients are often not only physically tired but mentally tired as well. The infection in children leads to a backward mental state. Patients have very little energy or initiative and are often considered stupid and lazy. Hypochondriasis is at times noted, and some severe cases become melancholic.

The Blood.—The red cell count averages in marked cases 2,000,000 to 3,000,000 red cells per cu. mm. The Hb. percentage is down in such cases to between 30 and 50. The color index is well below 1, except in certain rare cases, when the color index is that of pernicious anaemia, being above 1. These latter cases are very resistant to treatment and sometimes show very few infecting worms, notwithstanding the severity of the symptoms. There is at times a moderate leucocytosis, but as a rule the white count is approximately normal. Eosinophilia is quite characteristic and usually ranges from 15 to 35 per cent of the leucocytes. Eosinophilia tends to disappear as the cases become advanced.

The spleen and liver very rarely give rise to any symptoms and while albuminuria is rather common in advanced cases with oedema about the feet, yet casts are but rarely found.

Diagnosis

Clinical Diagnosis.—The diseases with which it is most likely to be confused are beriberi, chronic nephritis, and malarial cachexia. Stiles

* See p. 1273 (Bonne).

notes that heavy *Ascaris* infections may sometimes give rather similar symptoms. The signs of a multiple neuritis should differentiate beriberi, and the presence of casts or high blood pressure, chronic nephritis.

The cutaneous lesions may sometimes resemble and must be distinguished from those produced by the cercariae of certain *Schistosomes*. The "creeping eruption" of *Ancylostoma braziliense* is usually recognizable by the elevated, tortuous character of the tunnels in the skin. It may, however, resemble the lesions produced by invasion of the skin by larvae of warble flies of the genus *Gasterophilus*. Diagnosis of the latter affection may be made by extracting the larvae of the fly by massaging the skin lesion with oil, or by removing it with a needle and examining it under the microscope, and recognizing the black, transverse bands of the skin and body segments of the fly larvae.

In the Western Hemisphere, "creeping eruption" due to *Gasterophilus* frequently occurs in the same regions in which *A. braziliense* is encountered (Faust, 1940).

Laboratory Diagnosis.—The diagnosis can usually be made by finding hookworm ova in the faeces, usually by simple microscopical examination of films without concentration of the faeces.

However, Hsu and Chow (1939), who performed a series of autopsies in China, found hookworms in 117. Of these, stool examinations had been performed on 69 during life and in 44 of them no eggs were found. In 12 of the 25 negatives, only male worms were found. This report emphasizes the care that must be taken in the diagnosis of many cases.

The eggs are oval and thin-shelled, with a wide, clear, glassy zone separating the more or less segmented, granular central portion from the shell. If numerous, they can be found easily in ordinary fresh smear preparations by examination with the low power. If the infections are very light, concentration methods may be required to find the ova. For this purpose, Barber's technique is useful. On a slide emulsify a bit of faeces in equal parts of glycerin and saturated salt solution. The ova rise to the surface and can be recognized easily with a ⅔ inch objective. A larger amount of faeces may be emulsified in this mixture and centrifugalized. Put a wisp of cotton on the surface of the fluid. Pour on the cotton three or four drops of melted agar. Remove the disc of agar with the cotton and examine on a slide for entangled eggs.

Pepper and independently Lane recommended the following *"levitation" method*. The concentrated sediment of a centrifugalized specimen is transferred to a glass slide, mixed with 1 cc. of water and allowed to stand 5 minutes until the ova settle on the slide. The slide (kept in a horizontal position) is then immersed in water and gently manipulated until all coarse matter has floated free. The hookworm ova stick firmly to the slide (other ova do not). Lane reports that this gives about a tenfold concentration of ova.

Stoll's method of counting ova in the faeces is much used in estimating the heaviness of an infection and in checking the results of treatment. Weigh out accurately 5 Gm. of faeces and add enough N/10 NaOH to bring the volume to 75 cc. Make a *uniform* suspension by shaking vigorously at least one minute with glass beads. With a suitable pipette remove immediately exactly 0.15 cc., put on a 2 by 4 inch slide and cover with a 22 by 44 mm. cover slip. Using a mechanical stage count all the ova in the preparation. Multiply by 100 to get the number of ova per gram of faeces. This procedure is fairly satisfactory if ova are numerous but fails entirely if they are sparse.

Lane's D.C.F. (*direct centrifugal "flotation"*) *method* (1928) is regarded by many as the most efficient. This requires (1) special centrifuge tubes with flat bottom and ground off top; (2) 19 mm. square cover slips 0.5 mm. thick; and (3) special carriers with guards to keep the cover slip from slipping out of position. These are relatively inexpensive and can be used with any centrifuge. *Procedure:* (1) Measure exactly 1 cc. of faeces (either with Lane's special copper bucket, or by displacement of water in the (graduated) centrifuge tube) and put in the centrifuge tube. (2) Nearly fill the tube with water, stopper, and with the stopper down shake vigorously against the stopper

at least 100 times or until a *perfectly homogeneous* suspension is obtained. (3) Centrifugalize for 1 minute at 1000 r.p.m. (if the bottom of the tube is 6.25 in. from the center of the axis). (4) Decant carefully (about 3 per cent of the ova are lost with this fluid). (5) Nearly fill the tube with ¾ saturated salt solution (Sp. Gr. 1.150), and resuspend the sediment, avoiding air bubbles. (6) Fill just to the brim with the salt solution. (7) Carefully apply the cover slip which must touch the fluid and fit snugly on the top of the tube without leakage. A small air bubble may be expected. (8) Centrifugalize as before. (9) Lift the coverslip off quickly without tilting (the ova do not adhere to the glass in this salt solution). (10) Mount on a slide in a horizontal position, preferably on two small cones of plasticine so that the fluid does not touch the slide. (11) Count all the ova, using a mechanical stage and a magnification of 150. (12) Add a drop of salt solution so as to refill the tube, as in (7), and repeat the process.

According to Lane, on the average the first coverslip preparation contains 76 per cent of all the ova recoverable, and the second coverslip, 18 per cent. By repeating (7) to (11) twice more, an additional 3 per cent can be recovered, and the final 3 per cent by repeating the entire process with the fluid decanted in (4). Lane reports that this procedure gives more uniform and much higher egg counts than any other method, and that by it infection with a single female worm (if actively laying) can easily be diagnosed.

The same procedure is applicable to *Trichuris* and *Ascaris* ova, but fully saturated salt solution should be used.

Grassi estimated that each gram of faeces contained 15 ova for each worm, of which 25 per cent are males and 75 per cent females. Lane estimated that each female produced about 30 eggs per gram per day. The number of eggs per worm varies greatly, is less in heavy infections, and at best offers only a rough approximation of the degree of the infection.

Cultivation of the larvae (Baermann apparatus as described by Cort et al. 1922) is claimed by some workers to yield positive results more regularly than direct concentration methods. To the tip of a large (8 inch) funnel attach a short piece of rubber tubing provided with a pinch cock. Fill the funnel nearly to the brim with warm water and suspend on a suitable stand. Cover the funnel with a piece of wire gauze hollowed out so that it dips below the surface of the water. Cover the gauze with a single layer of towel. In the water in the middle of the cloth put the faeces (or soil) to be tested. Incubate for three days or more in a warm room. The larvae work out into the water and sink into the tip of the funnel. If a piece of ice is placed on top of the sample, it will hasten their migration. Draw off a few cc. of water, centrifugalize and examine the sediment for larvae. (Differentiate from *Strongyloides* larvae.)

The diagnosis can also be made by searching for the adult worms in the faeces after a vermifuge. They may be found in cases in which ova are not demonstrable in the faeces by the less efficient concentration method.

Charcot-Leyden crystals are often present in hookworm stools.

An *eosinophilia* (10 per cent to 20 per cent, occasionally higher) is usually present but is inconstant and may be absent in the severe cases.

Prognosis

The disease is more serious in children than in adults, on account of its interference with physical and mental development. The dark races do not seem to suffer as much as the white ones. Treatment is usually very beneficial, but in those who are debilitated by other diseases, or in those in whom the disease has assumed a pernicious anaemia tendency, the outlook is not good. In expectant mothers with low haemoglobin percentage, the prognosis is often grave.

The disease shortens the life of the people in an infected district and makes them readily fall victims to intercurrent diseases. Various sta-

tistics give the mortality as from less than one-half of 1 per cent to figures approximating 7 per cent.

PROPHYLAXIS

The first measure is to diagnose infections in all cases and to insist upon the treatment of such persons. The proper disposal of the faecal material from hookworm patients is the objective point in prophylaxis. Faecal contamination of the soil and water must therefore be prevented.

The use of some type of properly constructed privy is essential, as there is nothing more favorable to the development of the hookworm larvae from eggs to the infective stage than the practice of defecating on the ground where conditions of porous, sandy soil, shade and moisture exist. Later on, such a spot teems with infecting larvae and the person stepping there with bare feet is almost sure to become infected. For this reason, the wearing of shoes is an important prophylactic measure. At the same time, shoes are not a sure protection, as Ashford has noted infections in soldiers who wore good shoes, and infection may occur through the mouth from contaminated food or water. The faecal material should be buried not less than 300 feet from the water supply and down hill from the same. The best method is to use some septic tank process as the anaerobic processes of fermentation destroy the eggs.

The Chinese method of storing night soil for months in large cemented water-tight pits is favorable for destruction of the larvae, since under such conditions, with little air, the larvae soon die. However, it is important that there should be no mixing of fresh faeces with earth. The water supply must be carefully guarded from all possible sources of faecal contamination. Drinking water, unless above suspicion, should be boiled or filtered.

Hookworm disease tends to disappear in towns or cities where there is an efficient sewage system. The disease is one of the most conspicuous examples of soil pollution disease. Some authors think *Ancylostoma* more difficult to expel than *Necator*.

Scott (1937) in Egypt, found that over most of the country about half of the rural people are infected, although this proportion varies in different villages, going as high as 90 per cent in some instances. However, in certain districts, especially to the north of the delta, less than 20 per cent are infected.

In connection with the epidemiology of the disease in Egypt, the intensity of infection, by egg counts as compared with the percentage prevalence, is everywhere very low as compared with most countries where the prevalence is equally high.

The acquisition of the infection was markedly associated with field work. The rate of acquisition of hookworm infection was independent of the types of crops grown in various districts or of the different methods of irrigation in use. While soil polution was found to be very common throughout and immediately surrounding Egyptian villages, out of hundreds of specimens of soil from these localities no hookworm larvae were isolated. This failure of development was explained by the excessive dryness of the soils, the hard-packed nature of the surface, and the fact that most village soils inhibit the development of larvae even in cultures where the physical factors are held near their optimum values. This inhibition was tentatively attributed to the presence of excess chlorids, or any associated factor. Fine clay soils do not commonly serve as good media for developing hookworm larvae. Even with irrigation, the moisture contained frequently falls fairly low on the surface, and under such conditions the hot sun may kill many larvae.

Scott emphasizes that there is no evidence of any factors tending to maintain the intensity of human infestation in Egypt at the observed low level other than the influence of the low soil infestation intensity. It appeared that in lands under basin irrigation much of the hookworm infection was probably acquired during the season of rising flood water. Defecation in the fields was generally found to be scattered and therefore the risk of acquiring heavy infections at any one time were minimized. It would appear, then that in Egypt the climate, the physical and economic conditions of the

soils, and the defecation habits of the people are the controlling factors in maintaining hookworm infection at a low level of intensity.

In connection with soil transmission, it is interesting to note that in the Transvaal, where in many localities Ancylostomiasis is exceedingly prevalent, it is only found in alkaline mines and not in the acid ones.

Treatment

In the treatment of the disease, it should be recalled that the hookworms take blood, and so iron, from those who harbor them, and this is the first step in the production of hookworm anaemia. This loss of blood and iron may be overcome through the body supplying the blood-making marrow with iron from the food, or from that stored in the body, and this is the second step in the process. However, when this loss of blood has gone so far that it can no longer be compensated in this way, and in spite of this process serious anaemia is present, by prescribing iron for the patient the anaemia may still be reduced, even though the hookworms may remain present. Rhoads, Castle, Payne and Lamson greatly reduced the anaemia in hookworm cases by adding iron and liver to the diet. However, in many of the cases with severe infection, if not all, the haemoglobin will either not return to normal or remain at normal, unless the parasites have been first expelled.

Hence in the proper treatment of hookworm anaemia, as in hookworm infection, the first step should be the expulsion of the worms by treatment. Only in a very few cases with advanced anaemia, who are so ill that it may be regarded as unsafe to administer an anthelminthic, should iron be supplied first.

Anthelminthics.—The drugs which have been used most extensively and especially recommended for treatment of hookworm infection are (1) thymol, (2) betanaphthol, (3) oil of chenopodium, (4) carbon tetrachloride, (5) tetrachlorethylene, and (6) hexylresorcinol.

Thymol has been employed for many years and is still recommended by a number of physicians, notably by Clayton Lane (1932). The dosage recommended for an adult man is 60 grains (4 grm.); 3 doses of 20 gr. each in rice paper cachets; for an adult woman, 45 grains, and 20 grains in pregnancy. It should be given on an empty stomach and not given more than once a week. In advanced helminthiasis with great debility it must be used with great caution. For children under 5 years the dose recommended is 8 grains (0.51 grm.). From 5–10 years, 15 grains (0.97 grm.). At times the drug produces unpleasant forms of intoxication. It is definitely contraindicated if gastritis, dysentery, nephritis and active heart disease exist.

Betanaphthol has been recommended in doses of 3–10 grains (0.2–0.65 grm.). In larger doses it exercises an irritant action on the kidneys and may give rise to acute inflammation. Serious sequelae and even death have followed its use.

Oil of chenopodium was found by Darling and his associates (1920) to be more efficient in treatment than thymol. However, oil of chenopodium is quite toxic and is now not recommended except when given in conjunction with carbon tetrachloride, or tetrachlorethylene, for mixed infections of *Ascaris* and hookworm. The maximum tolerated dose of oil of chenopodium is 3 cc. for adults and 3 minims per year of age for children. However, the maximum therapeutic dose of the drug at times approaches the minimum lethal dose. Its use is contraindicated in nephritis, organic heart disease, diseases of the liver, respiratory infections, and pregnancy. Deaths may occur unexpectedly, especially in children, from oil of chenopodium (see Treatment of Ascaris

p. 1228). Smillie believes it is safer to give 0.5 cc. to a child in a tablespoonful of castor oil.

Carbon tetrachloride (CCl_4) (tetraform), a drug closely allied to chloroform, was first introduced by Hall in 1921 for human use as a vermifuge. It has since been employed for the treatment of hundred of thousands of hookworm cases with success. The drug has a high degree of efficiency and is usually well tolerated. Its adminstration is contraindicated in cirrhosis of the liver, in those with deficiency of blood calcium, alcoholism, respiratory infections and nephritis. Also, it is inadvisable to give it in the presence of *Ascaris* unless accompanied by oil of chenopodium. *Ascaris* may remain and obstruct the intestine. The recommended dosage is 30–40 minims (2–3 cc.) for adults and 2 minims (0.13 cc.) per year of age for children. This drug, on account of its ready availability, cheap price, and general efficacy, is still being widely employed. However, it has occasionally caused death. Smillie (1939) is among those who have reported deaths following its administration. Other recent deaths have been reported by several other clinicians.

Tetrachlorethylene (C_2Cl_4) has been more recently introduced as a specific for hookworm by Hall and Shillinger, in 1925. This drug is said to be free from most, if not all, of the toxic properties of carbon tetrachloride, and there are records of its having been used in hundreds of thousands of cases without any more unfavorable effects than slight nausea and dizziness and a transient burning sensation in the pit of the stomach. Lambert, in the South Sea Islands, has treated over 20,000 cases with no reports of deaths. The recommended dosage is the same as that for carbon tetrachloride, 3 cc. for an adult and 3 minims per year of age for children. Faust (1940) states that tetrachlorethylene is probably the drug of choice in the average hookworm case, either in the hospital or in the clinic.

Hare and Dutta (1939), in a comparative study of oil of chenopodium and tetrachlorethylene as anthelminthics, found that tetrachlorethylene in a dose of 4 cc. cured 10 times higher percentages than did oil of chenopodium of guaranteed BP strength in a dose of 30 minims. They regard the former as the better drug for all reasons. Oil of chenopodium was given in 20 minim doses to 17 cases. None were cured. In 30 minim doses, it was given to 84; 4.8 per cent were cured. Tetrachlorethylene, 4 cc. was given to 87 cases; 48.3 per cent were cured.

In administering the anthelminthics discussed above, purgation of the patient should be obtained the night before, preferably by the use of 30 gms. of sodium sulphate in a half glass of water. This purgative is recommended as being less toxic than magnesium sulphate if absorbed by the intestinal wall and in addition dissolves mucus surrounding the heads of the parasites, as well as decreases the absorption of carbon tetrachloride. In no case should oil for purgation be administered.

In the morning, the patient should remain in bed, abstain from food, and only coffee, tea, or water be permitted The prescribed drug to the amount indicated should then be taken.

Oil of chenopodium, carbon tetrachloride, and tetrachlorethylene may be administered in gelatin capsules, or in a spoon, mixed with sugar.

Two hours after administration of the drug, a saline purgative should be administered, and food allowed only after the bowels have moved freely. The faeces should be examined after 3 days to estimate what percentage of the worms have been expelled. It should be noted that while dead hookworms are apt to be found in the first stool passed, the parasites may continue to appear for more than 3 days after treatment. Eggs of the parasite may remain in the intestine for at least a week after treatment,

even though it be effective. If the infection has not been entirely eliminated, treatment may be repeated after one week.

Hexylresorcinol (1:3 dihydroxy-4-hexylbenzol), another anthelmintic, recently has been recommended and it is a less toxic drug than carbon-tetrachloride. It is a white, waxy crystalline substance, sparingly soluble in water, but exceedingly so in alcohol or vegetable oils. It was introduced as an anthelminthic by Lamson, Ward and Brown. It is now prescribed in hard gelatine capsules or crystoids. It is said that the drug has generally about a 75 per cent efficiency for hookworm, and that it is non-toxic when administered according to the instructions and is a particularly valuable drug for use in patients who are critically ill with the disease, or where other drugs are contraindicated, since the treatment may be repeated at 3-day intervals.

Lamson recommends insistence upon the following directions: the light evening meal should consist of soft foods only and the following morning the drug should be given on an empty stomach. The gelatin covering of the crystoids should not be broken by the teeth, since this may cause irritation from the oil to the buccal or oesophageal tissues. To avoid this, the crystoids must be swallowed whole with a glass of water. The dosage for adults and children over 12 years of age is 5 pills; for children of 8 to 12 years of age, 4 pills; for 6 to 8 years, 3 pills; under 6 years, 2 pills. The pills contain 0.2 grm. (3 gr.) each and the indicated number should be taken in one dose with the glass of water. No food of any kind should be taken for at least 4 hours after treatment. Water may be taken freely, but alcohol is definitely contraindicated.

After 4 or 5 hours following treatment, the patient may do as he desires and pursue his usual occupations.

A saline purge should be given 24 hours after treatment. The patient may continue to pass worms for as long as 10 days or 2 weeks after this single dose. If the instructions regarding food are carefully followed, one dose is usually sufficient.

Faust states that in children harboring a thousand or more worms, the infection may be reduced below clinical grade in 3 courses of treatment.

Treatment of the Anaemia.—The two factors—(1) chronic loss of blood, and (2) deficiency of blood-building materials—undoubtedly in time induce a hypoplasia, or even an aplasia of the marrow, and when this is well established the mere removal of the worms will not cure the anaemia.

For treatment then, first remove the worms and administer large doses of iron. Insure a well-balanced diet, containing meat protein, lipoids, and vitamins. Liver may be included with advantage. As to the iron, Ferris reduction, Blaud's pills (ferrous carbonate, or iron ammonium citrate) by mouth or intramuscular injections are both satisfactory. Wills (1936) and Meleney (1940) recommend the soluble ferrous salts as being most effective (ferrous sulphates), in dosage of 12–15 grains daily. Others recommend 20 grains. Whipple and his associates (1936) in the grave anaemia of dogs, found that iron given intravenously will be practically completely utilized and returned as haemoglobin, when iron given by mouth does not result in such proportional haemoglobin production—in fact in only 35 per cent. He found no difference in the ferrous and ferric salts. Wills, however, thinks injections of iron hazardous, because the therapeutic dose is close to the toxic dose. Once the anaemia is induced and the iron reserves depleted, this state will continue if the normal gastric juice is lacking. Hydrochloric acid is then indicated.

Heath (1936) emphasizes the importance also of normal intestinal absorption for the prevention of anaemia. In chronic diarrhoea, from whatever cause, iron deficiency

The infection has been encountered in human beings, particularly in northern Nigeria where it was reported in about 4 per cent of the prisoners in the jails (Leiper). Brumpt also reported a case on the River Omo in Africa.

The symptoms are produced by the larval forms becoming encysted in the muscularis and submucosa, usually in the large intestine. Gradually the parasites develop, and at the time of maturity the cyst is ruptured and the nematodes escape into the lumen of the intestine. The ruptured cysts are then likely to become invaded by intestinal bacteria, which may give rise to inflammatory processes resulting in ulcerations, peritonitis, and even perforations.

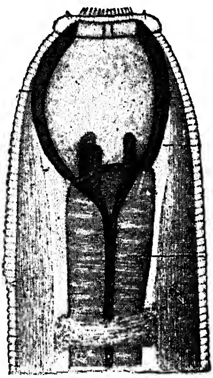

FIG. 285.

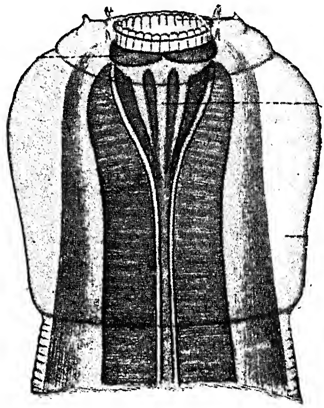

FIG. 286.

FIG. 285.—*Ternidens deminutus.* Head showing mouth capsule surrounded by a crown of leaflets. (After Leiper from Mense.)

FIG. 286.—*Oesophagostomum.* Head showing crown with leaflets at the entrance of the mouth capsule. Note bladder-like thickening of the cuticle around the anterior extremity. (After Raillet and Henry from Mense.)

A closely related species *O. stephanostomum* (Railliet and Henry, 1909) was discovered by Foy in a West African native. In general characteristics, it resembles *O. apiostomum*, but its measurements for both sexes are nearly double that size. It also has a corona radiata provided with 38 leaflike spines (var. Thomasi). In the case reported by Thomas in Amazonia in 1910, he stated there was no doubt that the patient died from septic peritonitis due to the lesions caused by the nematodes. It has also been found by Joyeaux in French Guinea and by Johnson (1933) in northern Nigeria. If the infection is severe, the parasites may give rise to dysenteric symptoms.

Syngamus laryngeus (Railliet, 1899), (*S. kingi*, Leiper, 1913), (*S. cyathostoma* of St. John, Simmons and Gardner, 1929).—A few cases of human infection with Syngamus have been reported, the first an Irish woman at Santa Lucia, West Indies, in whose sputum a pair of the worms were recovered by Leiper (1913). Two cases have been reported by Travassos (1921), and Lent and Pena (1939) from Brazil; 1 from the Philippines by St. John (1929); 1 from Trinidad; and 2 from Puerto Rico, Hoffmann (1932). All of these infections were apparently accidental, with the parasite *S. laryngeus* of the bovine species which parasitizes the upper respiratory tract of cattle, water buffaloes, and goats in the Orient, Puerto Rico, and South America. Buckley, however, believes that Leiper's specimens should be recorded as *S. nasicola*, of which goats are the usual host. Very little is known of the life cycle, though Buckley (1934) believes that an intermediate host is required. The worms in the trachea produce

irritative symptoms, usually accompanied by hemoptosis and at times asthma. Discharge of the parasites in the sputum after violent attacks of coughing or recovery of the eggs in the sputum provide means of diagnosis. Treatment in man has not been studied. Infection is probably acquired through infected uncooked food or by contaminated water. Other species of the genus have also been found in the upper respiratory tract of birds.

Morphology.—In the mammalian species the thick walls and buccal capsule is directed anteriad and is armed in its inner base with 8 subequal teeth. It is provided with a thick, muscular wall down to its junction with the oesophagus. Immediately around the oral opening there is a thick cuticular annulus around which there are a pair of broad dorsal and ventral petal-like lips and a pair each of dorsal lateral and ventral lateral lips. The male worm is considerably smaller than the female, and is permanently joined in copula with her. In the mammalian species the eggs are ovoidal and uncapped but in the avian species the eggs are provided with polar caps.

TRICHROSTRONGYLIDAE

Trichostrongylus colubriformis Giles 1892 (*Strongylus subtilis*) is normally a parasite of sheep and goats. It resembles the hookworm in its life cycle. Anteriorly it tapers to a pointed head end which is only one-tenth the thickness of the posterior extremity. The mouth is unarmed. The male (4 mm. long) has 2 prominent equal spicules. The females (6 mm. long) greatly outnumber the males. The vulva is in the posterior quarter of the body. The ova (42 by 70 to 90μ) resembles hookworm ova but are more translucent, and segmentation is much more advanced when passed. The parasite has been found frequently in man (in the small intestine) in Japan, India, Egypt and Central Africa and has been reported in man in Hawaii by Hall. Chandler found the parasite in 10 per cent of the cases examined in Assam. It may be anticipated in the United States, since sheep here are infected. The infection is usually symptomless, although it is reported that heavy infections may cause severe secondary anaemia. One case of human infection in the United States has been reported in Louisiana by Schenken and Moss (1938) in which, however, the diagnosis was made from the single male parasite which was found in the normal appendix removed. *Enterobius* was also present.

The infection occurs by the filariform larva that develops from the rhabditiform larvae which hatch from eggs in the soil. These enter the body by way of the mouth. The adult parasites live with their heads embedded in the intestinal mucosa of the small intestine. The diagnosis may be made by recovering the characteristic eggs in the faeces. Manson-Bahr reports that these worms can be expelled by treatment with carbon tetrachloride.

Haemonchus contortus (Rudolphi, 1803).—This is a very common intestinal parasite of sheep but at least several cases have been reported for man; 1 in Brazil and 3 in natives in Australia. Males are about two-thirds inch long (15 mm.) and females about 1 inch long (25 mm.). The anterior end shows 2 tooth-like papillae directed dorsad. The adult worms are distinguished by the single curved lancet (blood hooklet) in the depth of the small buccal cavity. In sheep the infection produces a serious manifestation with marked anaemia and emaciation. The ova passed in the faeces are very difficult to differentiate from those of other Strongylate worms and an accurate diagnosis can be made only after recovery of the adult worm following an anthelminthic treatment, or autopsy. Faust (1940) states that carbon tetrachloride is not effective in tolerated doses and tetrachlorethylene must be administered repeatedly in large doses to produce good results. Infection occurs through the ingestion of vegetation upon which the third stage infective larvae have crawled.

METASTRONGYLIDAE

Metastrongylus apri (-*Metastrongylus elongatus*, Dujardin, 1845), (*Strongylus apri*, Gmelin, 1790).—This nematode is a common parasite of hogs, occurring in the bronchi and causing a bronchitis which may be fatal in young animals. It has been reported 3 times in man.

The male is about 1 inch (25 mm.) long, with 2 long spicules. The female is about 2 inches long and has a sharply hooked posterior extremity with the vulva just beyond the bend. The mouth has 2 lips, each with 3 lobes. The eggs contain embryos when laid. It probably does not require an intermediate host.

DIOCTOPHYMOIDEA

Large worms characterized by males having a closed, bell-shaped caudal bursa without rays. Mouth hexagonal with 6 to 18 papillae. Oesophagus very long, without bulb. Family DIOCTOPHYMIDAE.

Dioctophyme renale (*Eustrongylus gigas*), the kidney worm of the dog, may rarely attack man. About 9 authentic cases have been reported. In many of the reported cases fibrinous clots from the ureters or wandering round-worms were mistaken for this parasite. It is usually found in the pelvis of the kidney. One or more of the worms may so distend the kidney as to convert it into a mere shell. Pain, haematuria, together with the finding of the eggs in the urine, determine the diagnosis. The parasites may produce acute uraemic poisoning. Surgical removal of the worms and appropriate treatment of the damaged kidney are the only known therapeutic procedures. The eggs are 40 by 65μ, brownish yellow, ellipsoidal, with a thick shell marked by pitted depressions except at the poles. It is the largest of the parasitic round worms, attaining a length of 3 feet and the thickness of a man's finger, and has been called the giant strongyle. The male is about 10 inches long.

The collar-like copulatory bursa of the male distinguishes it from *Ascaris*, as does the dark red color. Infection is probably acquired by eating raw fish.

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Chapter XLV

STRONGYLOIDIASIS

and Minor Helminthic Infections

Infection with *Strongyloides stercoralis* of the superfamily *Rhabdiasoidea.* The superfamily is characterized by having two heterogenetic generations, one of free-living rhabditiform males and females and one of parasitic, filariform females. Family STRONGYLOIDIDAE. Genus *Strongyloides grassi*, 1897.

Strongyloides stercoralis, Bavay, 1876.—This parasite is especially common in Cochin China and Brazil, but is widely distributed in tropical and semi-tropical regions and is fairly common in the southern United States. It is occasionally encountered in temperate regions.

History.—The writer detected, in 1897, and reported in Baltimore at the Johns Hopkins Medical Society the first case encountered in North America. Thayer (1901) also reported 3 cases, two of which apparently originated in the southern United States. The parasite was first found by Norman (1876) in the faeces of French colonial troops suffering with what was known as "Cochin China diarrhoea." Bavay, at Norman's suggestion, undertook a careful study of these cases and named the parasite found in the faeces *Anguillula stercoralis.* Five of the cases resulted fatally and at autopsy minute nematodes of a species apparently different from those found in the faeces were discovered in the wall of the ileum and in the biliary and pancreatic ducts. The form found in the intestine was named by Bavay *Anguillula intestinalis* to distinguish it from the form found in the stools (*Anguillula stercoralis*).

Roux and Laveran, discussing the role played by *Anguillula stercoralis* in Cochin China diarrhoea, concluded it was probably the cause of the disease.

Studies by Grassi (1879), Perroncito (1880), and particularly Leuckart (1882), demonstrated that the two forms of the parasite named *Anguillula intestinalis* and *A. stercoralis* constituted only different stages in the life cycle of a single parasite, the cycle being heterogenetic and having both a parasitic and a free-living generation. Later it was shown that there were two types of life cycle, one with a direct development, the other with an indirect, heterogenetic one. Lichtenstein (1899) favored the view that there were two distinct strains, the direct one developing in temperate zones and the indirect one in the tropics. Evidence in favor of this view was brought in 1897 by the writer and by Thayer (1901), and by the writer in the Philippines in 1900.

In 1897 in Baltimore, and in 1900 in the Philippines, the writer demonstrated by the study of stained sections of the small intestine that the adult parasitic females lived in the intestinal wall, where they gave rise to a catarrhal inflammation with desquamation, and in many places atrophy of the epithelial cells, and sometimes with an increase of eosinophiles in the tissues. The eggs containing larval forms were laid in the mucosa and when hatched the larval forms passed into the lumen of the bowel. Later Askanazy (1900), in the study of fresh specimens, confirmed the fact that the adult parasites live in the intestinal wall and still later demonstrated this in preserved sections.

In severe infections, the lesions of the intestines were regarded by the writer as the cause of the diarrhoeal attacks, partly produced by the mechanical action of the parasites and the products of their metabolism.

Following the discovery of the life cycle of the hookworm, Looss (1899–1905), Fulleborn (1914), and others, showed that the infective

stage larvae of *Strongyloides* also might enter the body by way of the skin, passing through the blood stream to the lungs, entering the air sacs, ascending the respiratory tract to the epiglottis, and then after being swallowed, on arriving in the intestinal tract develop into the parasitic generation.

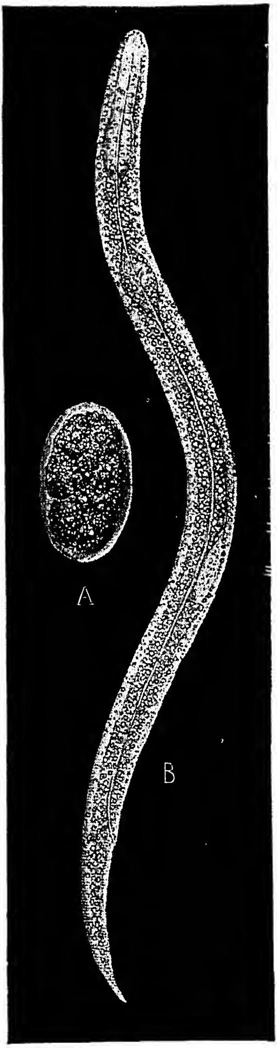

FIG. 287.—A, Egg of *Strongyloides stercoralis* (parasitic mother worm) found in stools of case of chronic diarrhoea; B. Rhabditiform larva of *Strongyloides stercoralis* from the stools. (William Sydney Thayer, in Journal of Experimental Medicine.)

In the study of the life history of the parasite outside the intestine, i.e., the free living generation of the indirect type, both adult males and females were found. However, up to 1932, in the parasitic generation only females had been observed, which led to the generally accepted opinion that the parasitic females were parthenogenetic. But in 1926 Sandground reported the presence of spermatozoa in parasitic females of *Strongyloides ratti* and suggested that syngamy existed in the genus *Strongyloides*. Kreis, in 1933, next reported the presence of rhabditoid parasitic males in the faeces of man, as well as of a dog experimentally infected with *S. stercoralis*. Later these adult males were reported as rare in the intestine but more frequent in the lungs. Faust (1933) confirmed the discovery of males in experimentally infected dogs and has reported upon the development and differentiation of the two sexes of the parasitic generation from the time they enter the skin or buccal mucosa until they become mature in the intestinal tract. Blacklock, 1938, points out that it is very difficult to distinguish the adult parasitic male from the free living male form.

Geographical Distribution and Incidence.—The parasite seems primarily adapted to warm climates, but is reported from time to time sporadically in temperate ones. It is common in the Far East, as in Cochin China and the Philippines; in the Western Hemisphere it has been reported as common in Brazil (Sao Paulo, Amazonia), in Panama (23 per cent) and Colombia (16 per cent) and Puerto Rico (35 per cent). Willets found an incidence of 20 per cent in Georgia, and Wood of 15 per cent in Mississippi. In other parts of the southern United States, Hinman (1938) found it varied from less than 1 per cent to approximately 5 per cent. Faust (1934), in hospital cases in New Orleans, found a 4 per cent incidence. Hinman also found the incidence in an institution in Louisiana to be 4.8 per cent, while Cable (1936) found 2.7 per cent of infection among students in Kentucky. It is common in tropical Africa and in regions of the Congo. Ostrom reported an incidence of 23 per cent. Typically the disease seems to be more common in the moist tropical regions.

Morphology and Life Cycle.—The *intestinal form*, formerly known as *Anguillula intestinalis*, a female long regarded as parthenogenetic, lives deep in the mucosa of the jejunum. It is about 2.5 mm. long and 40 to 50μ wide, has a pointed three-lipped mouth and a filariform oesophagus one fourth the length of the body. The anus is near the sharp posterior end and the vulva near the posterior third of the body. The double uterus occupies the middle and posterior thirds of the body and contains a row of

8 to 10 large elliptical eggs nearly as wide as the parent worm. The worm is so translucent that it is difficult to detect it in the mucosa, even with a hand lens. The mucosa should be scraped off and the preparation searched with a ⅔ inch objective.

The ova when discharged from the vulva closely resemble hook worm ova but are strung out in a chain by a thin transparent sheath-like membrane and might possibly appear in the faeces, but this occurs usually only after brisk purgation. Segmentation is well advanced, however, and normally the ova quickly give rise (in the intestine) to *rhabditiform larvae* about 250μ long and 13μ broad, characterized by a double oesophageal bulb. They closely resemble the corresponding stage of hookworm larvae which may hatch in incubated stools, but the depth of the mouth cavity anterior to the oesophagus is only one third the width of the larva, while in the hookworm larva it is about equal to the width. The rudimentary genital organ is conspicuous and about 20μ long, while in the hookworm it is small and inconspicuous (Figs. 277 and 279). *Almost invariably fresh faeces contain larvae in strongyloid infection but only ova in hookworm infection.*

The larvae grow rapidly and at suitable temperatures (over 25°C.) may develop in 3 to 5 days into *free-living males and females.* Both retain the rhabditiform oesophagus. The male is about 750μ long and 40 to 50μ wide and has an incurved tail and two spicules. The female is about 1 mm. long, 50 to 60μ wide, with an attenuated tail and a double uterus containing several ova. Following copulation (in the faeces outside the body) the ova are discharged and quickly give rise to *rhabditiform larvae* identical in appearance with those of the preceding generation hatched in the intestine. These develop in 3 or 4 days into *filariform* larvae about 0.6 mm. long, with a simple tubular oesophagus, the infective stage. (*"Indirect"* or *heterogenetic cycle.*) These are distinguished from the corresponding stage of hookworm larvae by the length of the oesophagus which in *Strongyloides*, is one half instead of only one quarter of the length of the body.

If the temperature is below 25°C. or as a result of other conditions not yet understood the rhabditiform larvae (arising in the intestine from the parasitic female) develop in the faeces directly into infective filariform larvae, skipping the sexual stage. (*"Direct" cycle.*) Faust has suggested that larvae from fertilized ova develop indirectly, while those from unfertilized females develop directly. Others believe that the directness or indirectness during the free-living phase is contingent solely upon environmental factors, optimum conditions producing continuous free-living *rhabditiform* generations while unfavorable ones shorten free-living developmental metamorphosis.

However, Graham (1939), who has been able to develop strains of *Strongyloides ratti* after exposing experimental rats each to a single infective stage larva, has concluded from his comparison of homogonic and heterogonic lines that the former produces a predominantly direct type and the latter a predominantly indirect type of progeny.

It has been claimed recently that under certain conditions some of the rhabditiform larvae may develop in the intestinal contents into infective filariform larvae without the usual period of growth outside the body. (*"Hyperinfective" cycle.*) These are said to penetrate the intestinal wall and immediately go through the usual developmental cycle, superinfecting the host.

Faust and deGroat (1940) point out that Grassi and Segre and Leichtenstern found it necessary to postulate self infection (autoinfection) in order to explain the long continued presence of *Strongyloides* in human cases. Later Fülleborn was unable to produce internal auto-infection in experimental mammals and sponsored the theory of peri-anal self infection. Fülleborn was convinced that soiling of the peri-anal skin with the infected patient's moist faeces containing rhabditoid larvae provided the opportunity for them to metamorphose into the filariform stage and enter the body percutaneously. Therefore a number of helminthologists have regarded internal auto-infection with considerable scepticism. However, several Japanese investigators and Faust and his associates have reported that they have been able to accomplish experimental auto-infection. It seems possible that rhabditiform larvae which hatch and remain in the bowel wall for any length of time may be transformed into filariform larvae and that these may cause auto-infection.

Brumpt (1936) has shown by experimental infection on himself that *Strongyloides vituli* (a species found in the calf) and *S. ratti* of rodents, while not capable of parasitizing man yet when the larvae are placed upon the skin they give rise to a violent pruritis with local urticaria, a papular eruption, and oedema, which may last for a month.

Pathology

After arrival in the intestine, the young females of the parasitic generation rapidly mature and infect the tissues of the mucosa. The portions of the intestine most commonly parasitized are the duodenum and upper jejunum. However, all portions of the intestine have been found infected, from the pylorus of the stomach to the anus. Only adult females have been found penetrating the mucosa. They penetrate all layers of it and have occasionally been reported as migrating below the muscularis mucosae. Whether the penetration into the muscularis mucosae occurs antemortem in human beings is questioned. The ova are found especially towards the base of the villi, or between the glands, where they are found single or in nests. Upon hatching, the young larvae pass towards the lumen of the intestine. The writer has in some instances demonstrated them in sections beneath the epithelium of the villi. A microscopical study of sections of the small intestine invaded by the parasites often shows a catarrhal inflammation with desquamation and in many places atrophy of the epithelial cells. Solitary follicles are often slightly swollen and there are infiltrations of small round cells about the glands.

There may be in very severe infections an increase in the eosinophiles about the areas which contain the parasites or ova. However, this is not always demonstrable. In the crypts of Lieberkuhn containing eggs and embryos at the bottom, the epithelium is much compressed and often atrophied. The epithelial cells are also compressed and atrophied in the cysts containing several ova. In sections where the egg has hatched, and the embryo escaped, the epithelium on one side of the crypt has sometimes disappeared. There are frequently infiltrations of small round cells about the adult parasites and desquamation of epithelium is often marked about them. Not infrequently the embryos may be seen breaking through the crypts and lying between the epithelium of the villus (Strong 1900).

Faust (1935) has described the lesions which occur in the skin and the lungs in 62 experimentally infected dogs. He found petechial haemorrhages at the site of skin penetration of the larvae and intense pruritis accompanied their penetration. Infective larvae sometimes remain passively in the skin for several days. Brumpt (1936) and Hinman, each in experimental cutaneous infections of themselves, the former with *S. vitali* of calves *S. ratti* of rodents, and the latter with *S. stercoralis*, have experienced this pruriginous dermatitis. However, skin lesions appear to reflect a personal idiosyncrasy or allergy, for Sandground (1928), who acquired a massive laboratory infection with *S. stercoralis* which endured for more than 15 years and was accompanied by high eosinophilia (59%) and a persistent gastro-intestinal flux, informs the writer that cutaneous lesions never appeared even though he exposed himself on numerous occasions to the infective larvae of *S. ratti* and *S. fülleborni* of monkeys.

When the larvae arrive in the pulmonary cavity they penetrate into the alveoli and bronchioles. This may be accompanied by petechial or even more profuse haemorrhage into the air passages. About the larvae there is frequently a proliferation of epithelial cells and leucocytic infiltra-

tion in the air passages. Congestion sometimes apparently prevents the normal migration of the larvae up the bronchioles with the result that metamorphosis into the post-filariform, pre-adolescent, and adolescent stages may occur in the lungs. Oviposition may even take place here. Bronchial pneumonitis may result as a sequel. Adult worms lodged in the bronchial epithelium may give rise to a chronic bronchial disease. The extent of damage due to this pulmonary migration of the parasites in man is not known, but in 2 of 85 cases reported by Hinman (1938) a history of antecedent cough and bronchitis was elicited.

Barlow has reported a case with cough for 3 weeks and with signs suggesting a slight bronchial pneumonia, while Gage (1910) found the larvae of *Strongyloides* in the sputum in a case and DeLangen (1936) also reported the larvae in the sputum in two cases. It is probable that in man pulmonary lesions and symptoms are produced only by severe and massive infections.

Several Japanese investigators and also Nolesco and Africa (1936) and Torres (1938) in autopsy examinations, have demonstrated the larvae in the lungs.

Symptomatology

In severe infections the females and their larvae which give rise to the chronic catarrhal inflammation of the mucosa, especially by their mechanical movements and perhaps by the products of their metabolism, gradually cause a destruction of the epithelial cells which results in a diarrhoea which, however, rarely contains red blood cells. The degree of the diarrhoea seems to depend particularly on the intensity of the infection, its duration, and the susceptibility of the hosts. In the Far East, diarrhoea is frequently the most common symptom. Sometimes it alternates with periods of constipation. Barlow (1915) found in cases in the tropics that an uncontrolled watery diarrhoea with profound emaciation was the most conspicuous accompaniment of the infection. However, it should be emphasized that diarrhoea is not always present. Levin (1938), in the report of 29 cases, noted diarrhoea in 5, mucus and blood in the stools in 5, indigestion in 10, and abdominal pain in 13.

Hinman (1938), who studied 85 cases, found that 26 of the patients had diarrhoea, of which 14 had bloody diarrhoea during the course of the infection; 7 more had alternating diarrhoea and constipation; and 10 had constipation alone; 26 had lost weight, and in the cases where the loss was known it was found to average 14.5 lbs. per patient.

He found that abdominal pain was the chief complaint and more than one-half the patients were disturbed by it. The pain was variable, both in character and location. In 12 of 44 it was diffuse and crampy. In 13, it was found to be in the epigastrium. In 7 it was located in the right lower quadrant, and 5 in the right side of the abdomen. Loss of weight, vomiting, malaise, fever, weakness, and indigestion were less frequently complained of. Five of the patients were admitted with a tentative diagnosis of appendicitis. The highest temperature was 100°F. or less in 59 of 83 cases. In 14 it was between 100° and 101°F. and in 6 it was above 101°.

Blood.—Hinman found that a moderate secondary anaemia was frequently present. In only 6 cases was the white cell count above 10,000 per cubic millimeter, and only 1 below 5,000. The differential count showed an average eosinophilia of 8.6, with 14 cases above 10 per cent. Levin (1938), in the report of 29 cases, found an increase

states develop. Hence such symptoms when present should not be disregarded and additional appropriate treatment given to alleviate them.

For the treatment of larva migrans, see p. 1520.

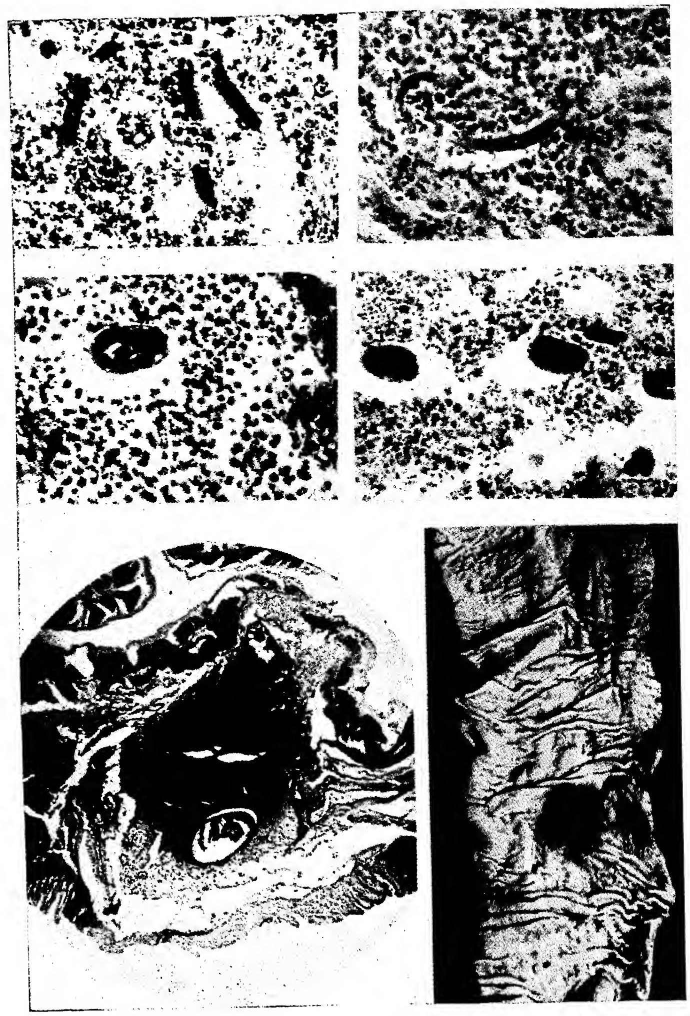

FIG. 284.—(After Bonne. Courtesy Amer. Jour. Tropical Medicine.)

Rarer Species of Hookworms in Man

Ancylostoma braziliense (de Faria, 1910), (*A. ceylanicum*, Looss, 1911), (*Agamonematodum migrans*, Kirby-Smith, et al, 1926), is a parasite of dogs and cats occurring in North and South America, and also in Ceylon, India, Siam and the Philippines. Human infection has been reported from these countries in association with other species of hookworms. The infective larvae may penetrate the human skin and burrow extensively through the subcutaneous tissue, causing a painful itching eruption

known as "creeping eruption" or "larva migrans" (common in Florida and other southern states, as well as in the other regions mentioned and already discussed p. 1264 and also in Chap. L). It is the smallest of the species of *Ancylostoma* (the male not above 8.5 mm., in length the female 10 mm.) and can be distinguished by the relatively much smaller inner pair of ventral teeth and by the shape of the dorsal ray of the caudal bursa, which is deeply cleft and each division again bifurcated. Figure 284 illustrates the lesions of the small intestine and the invasion of the submucosa by *Ancylostoma braziliense* in a native in Java. In this instance, reported by Bonne, the invasion resulted in peritonitis and death. Bonne (1942) subsequently has described 9 other cases. In the last 5 of these, infection of the intestinal wall was observed at autopsy in Batavia in which the invading species was *Ancylostoma duodenale*. *Necator americanus*, the most common hook worm in Java, does not show this invasive power.

Ancylostoma caninum (Ercolani, 1859) the dog hookworm. This species is common in dogs and cats, particularly in the northern hemisphere. It has been reported once as a parasite of man in the Philippine Islands (Manalang, 1925). The male has an average length of 10 mm., the female 14 mm. It has a wide buccal capsule to accommodate the 3 pairs of ventral teeth, a diagnostic character of the species. The eggs are similar to *A. duodenale*, but are slightly larger, 63×41 microns. This parasite has been used experimentally in the study of the action of hookworms.

Ancylostoma malayanum is an ursine species which has been found in India and the Malay States and has been reported once from man (Yorke and Maplestone, 1926). It resembles *A. duodenale* and its eggs are indistinguishable from it. Its chief distinguishing point is its larger size, the males being 12–15 mm. and the females 15–19 mm.

STRONGYLIDAE

Ternidens deminutus (*Triodentophorus deminutus*) is a small, round worm about the size of a hookworm. The terminal buccal capsule is surrounded by a crown of leaflets, while at the base are 3 forked teeth guarding the entrance to the oesophagus. The vaginal orifice is near the posterior tip. The ova resemble hookworm ova but are larger, 50 by 80μ, more segmented, and have broadly rounded poles and are somewhat flattened on one side. The parasite occurs in several monkeys and has been found not uncommonly in man in South Africa (Sandground, 1931, Blackie, 1932). Sandground found the parasite first in the United States in the faeces of a missionary from Africa who had been treated for hookworm infection previously. The parasite has also been encountered in East Africa. In parts of Southern Rhodesia, Sandground found 65 per cent of the natives infected. He found that the infective third stage larva is semi-rhabditoid in type, resembling that of *Oesophagostomum*, and is not infective by the skin route. This parasite inhabits the wall of the large bowel where it may produce cystic nodules. Carbon tetrachloride and tetrachlorethylene have been reported as moderately effective in evacuating the mature parasites.

Oesophagostomum apiostomum (Willath, 1891)—*O. brumpti*.—This nematode was first noted by the writer in monkeys (*Macacus philippinensis*) in the Philippines in 1900, and also occurs in other species of monkeys in China and in Africa, especially northern Nigeria and Central Africa. In length it resembles roughly a hookworm, but is somewhat smaller. In both sexes there is an ovoid expansion of the cuticle at the anterior end, which is limited in front by a salient oral ring and posteriorly by a constriction which is especially marked on the ventral surface 200μ distant from the oral vestibule· this in turn is provided with a crown of 12 sharp, chitinous plates directed forward and inwards. The male is 8–10 mm. in length by 0.35 mm. in breadth; the copulatory bursa has a dorsal ray which bifurcates into two branches, forming a horse-shoe-shaped structure: each limb gives off a short lateral horn near its base. The female is 10 mm. in length by 0.325 mm. in breadth. Posteriorly terminating in a sharp point; the vulva is situated in the anterior half of the body. The eggs are passed in an advanced stage of development, and measure 60μ in length by 40μ in breadth, and closely resemble those of Ancylostoma. The life cycle of this worm is probably as follows: the larvae (filariform stage) are swallowed and pass undigested through the stomach and small intestine, and on arrival in the caecum exsheath and invade the wall of the intestine where they cause nodule formation. The life cycle, however, has not been completely worked out for this particular species of Oesophagostomum.

This species was first found by Owen in gastric tumors of a tiger. It is normally parasitic in the stomach wall of wild and domestic cats, mink, and rarely dogs, forming hard, cystic tumors, sometimes 2–3 cm. in diameter and causing grave disturbances. They may open into the abdominal cavity and may cause fatal peritonitis.

The parasites vary in length; the males 11–25 mm., and 2 mm. in diameter; the females 25–54 mm. The cephalic end is expanded into a globular swelling armed with 8 rows of thorn-like hooks. The eggs (in faeces) have a plug at one end like a bottle stopper and are not segmented when deposited. They develop into larvae in a species of cyclops. The parasite is not well adapted to man as a host. No human cases in which the parasites are present in tumors of the intestinal tract have been observed. Daengsvang (1939) has reported from India an abdominal tumor caused by the parasite. In most human cases of infection, immature worms were found, with 4 or 8 cephalic rings of spines, which presumably had "lost their way."

The parasites have been found in abscessed pockets or indurated nodules with necrosis in the center. In other cases, they have been found in deep cutaneous or subcutaneous tunnels in which the worms were migrating, as in larva migrans, and presenting the condition which has been termed creeping eruption. (See Chap. L, p. 1520). The parasites have been usually discovered lying between the stratum germinativum and the corium with accumulations of eosinophiles, plasma cells, neutrophiles and mononuclear cells. The nodules have been observed in many parts of the body. Levinsen found them in breast abscesses. Maplestone found the parasite in an abscess between the right thumb and index finger and in another case on the surface of the temporal muscle in a patient with symptoms resembling mastoiditis. Maplestone and Bhaduri, in 25 cases analyzed, found swelling of the pharynx and dyspnoea in half. They point out that the swellings present, even when widely separated, usually cease on the removal of a single parasite.

The diagnosis can be made only after worms have been discovered and recognized. The migrating variety of the infection may sometimes be confused with other forms of furunculosis which may be caused by bacteria. In the migrating forms, the diagnosis may be confused with larva migrans caused by hookworm.

The treatment should consist of incision of the lesions and removal of the worms, with disinfection of the cavity.

Chandler found that encysted gnathstome larvae which are infective for cats are common in snakes in south-eastern Asia, and they probably occur in other animals. It is believed that human infection might be caused by eating raw snakes, a practice indulged in by some wild tribes in this region. Chandler, however, was unable to see how cats and snakes manage to pass the infection back and forth between them in nature.

Later it was shown that the ova becomes embryonated and hatches in water and develops in cyclops. Africa, et al, however, have shown that the encysted larvae are found in fresh water fishes in the Philippines and that infection occurs not by drinking water containing the infected cyclops, but by eating raw fresh water fish, infested with the larvae. It is presumed that the fish may become infected from ingesting infected cyclops. Frogs and eels found in fish markets in Siam have also been found to harbor larval *Gnathostomes*.

Thelazia

Thelaziasis.—*Thelazia callipaeda*, (the Oriental "eye worm") Ralliet and Henry, 1910 and *T. californiensis*, Kofoid and Williams, 1925. These slender parasites are perhaps more nearly related to the *Filariidae* than to the *Spiruridae*. They inhabit the conjunctival sac and lacrimal ducts, occasionally in man and more commonly in dogs. At times they creep over the eyeball, later returning to the inner corner of the eye. The former species has been found in India, Burma and China, while the latter has only been found in California in one human subject and also in dogs and cats in the same area. Other species occur in the eyes of other animals.

The female parasites measure from 7–19 mm. long. The males are somewhat smaller. The cuticle is pleated, with well defined striations with sharp edges. There

are no lips, but there is a short vestibule. The vulva is anterior as in *Wuehereria* and the male has no caudal alae. The life cycle is not yet known, but roaches have been shown to serve as intermediate hosts for *T. mansoni* in chickens. On ingestion of the cockroach by the chicken, the encapsulated larvae are set free and are presumed to migrate up the oesophagus, pharynx and lacrimal duct and come to reside in the canthus of the eye. In man the movements of the parasite in the eye cause considerable irritation, sometimes nervous symptoms and excessive lacrimation.

Faust (1940) observed that the movements of the parasites across the cornea with their cuticular striae produces at times minute scratching of the surface and that such chronic irritation may result in the development of opacities of the injured area. The movements of the parasites in the sac may produce excruciating pain.

Trimble attributed paralysis of the muscles of the lower eye-lid with ectropion to the presence of the parasites. Blindness is not infrequently produced by one species, in cattle in Africa.

The presence of creamy white thread worm masses, coiled in the conjunctival sac or migrating over the cornea are suggestive of the diagnosis. The worms are usually easily removed with forceps but several examinations may be necessary in order to remove all of them.

Cheilospirura sp. Africa and Garcia (1936) have found a parasite of this genus in a nodule in the conjunctiva of a Philippino. The infection is unusual, for previous species of this genus normally live in the lung or in the gizzards of birds.

The Gordiacea or Hair Worms (Hair Snakes)

These worms have a somewhat higher organization than the flat worms and are classified in the *Nemathelminthes*, a term meaning thread worms. In the mature state they have an atrophied digestive tract, a true body cavity, gonads discontinuous with other ducts and lack lateral lines and flame cells. The adult worms are free-living in water. The larvae are parasites in insects. Human infection is accidental. The adults are elongated, wiry parasites measuring from 10–50 cm. in length. Their anterior ends are bluntly rounded. The sexually mature worms mate in water where the eggs are laid in strings. The larvae which hatch from the eggs penetrate the body wall of various species of *Orthoptera* and other insects. After a metamorphosis they become Gordius-like worms. As they approach maturity they escape from the insect and become free-living forms. The popular name of "horse-hair snakes" comes from the popular idea that they develop from horse hairs that fall into water.

On several occasions when the adult worms have been passed from the intestinal tract *per anum* or have been vomited, Faust, 1940, states it is believed that either free-living adults or adolescent worms still within their insect hosts were accidentally swallowed in drinking water.

In earlier years, grave consequences were attributed to the presence of these parasites in the body. It is now believed that the symptoms attributed to them in the alimentary canal were due either to other causes or were psychological. However, in a case reported by Faust and his associates in which a juvenile female specimen of *Gordius* was recovered from the lower border of the orbit of a patient in Florida the worm was undoubtedly a tissue parasite and had set up considerable reaction in the surrounding tissues.

The Acanthocephala or Thorny-headed Nematodes

These are called thorny-headed worms because they possess a proboscis which projects anteriorly like a little peg and are armed with several rows of hooks which are directed backward and enable the parasite to attach itself to the intestinal wall. The worms absorb nourishment through the general body wall, there being no alimentary canal or mouth. They are probably more nearly related to the Cestoda than the Nematoda. Only the following species are known to be recorded for man.

Macracanthorhynchus hirudinaceus (*Gigantorhynchus gigas*) is normally an intestinal parasite of hogs. The male is 2–4 inches long (5–10 cm.), the female 10–18 inches

(24–45 cm.). The body shows transverse rings and resembles *Ascaris*, but is more white in color. The eggs, which are brown in color and about 80–100μ long, contain embryos with 2 pairs of large hooks at the anterior end and a spiny body. The intermediate hosts are larvae of June bugs and related beetles, and various species of white grubs.

Human infection was formerly considered to be common in south Russia (Lambl, 1859 and Lindemann, 1865). Lindemann stated that at that time the infection was common in the Volga valley, where Schneider found the beetle, *Melolontha*, was eaten raw. More recently Russian investigators have found pigs infected, but no further human cases. In pigs, as a result of multiple infection, considerable inflammation is frequently found at the site of the attachment of the parasite to the intestinal wall and not infrequently perforation of the intestine has occurred.

Moniliformis moniliformis, Bremser, 1811 (*Gigantorhynchus moniliformis*), an intestinal parasite of rats, has been reported in man in a few cases. Human cases of infection, apparently authentic, have been reported from Italy, the Sudan, and British Honduras. Calandruccio infected himself experimentally with this parasite. Beginning on the 19th day after infection, he experienced serious gastro-intestinal pain, diarrhoea, exhaustion, somnolence, and tinnitus aurium. The parasites, however, did not become sexually mature until 5 weeks after the time of infection. Under treatment with aspidium filix-mas, the parasites were evacuated and the symptoms completely disappeared after 48 hours.

The parasite might be contracted by eating "death watch beetles," as is sometimes done with the idea of improving the complexion. The male is 2 inches (5 cm.) long, the female 4–10 inches (10–25 cm.). The proboscis has 12–15 rows of hooks. A beetle, *Blaps mucronata*, and the cockroach, *Periplaneta americana*, are the intermediate hosts.

ANNELIDA

Leeches belong to the most highly organized group of worms, the Annelida, of the class Hirudinea. Members of this class are parasitic or semiparasitic and do not possess chaetae, but move about by means of a sucker at the posterior end. They are to a considerable degree sanguinivorous and have a mechanism adapted for the engorgement of relatively large amounts of blood.

They have a rather oval body marked by numerous rings, and well developed muscular system, which enables them actively to contract and extend. In addition to the sucker at the posterior end there is a sucker at the anterior extremity. Within this is the mouth leading to the pharynx, which by the action of its muscular walls serves as a pumping organ. The salivary glands, situated inside the mouth cavity, secrete the fluid which prevents coagulation of the blood. The mouth may or may not be provided with cutting jaws. In *Hirudo* there are 3 semicircular jaws, the arched surfaces of which are beset with from 50 to 100 sharp teeth. The mark of a leech bite is triangular. When a leech has gorged itself, it becomes detached from the skin of its victim, but the effect of the salivary secretion in retarding coagulation is of some duration so that the wound continues to bleed. With some of the leeches, the wounds frequently become infected and ulcers, which may prove serious often result. This is particularly true with *Haemadipsa zeylanica*. This species is a land leech, but requires abundant moisture. However, many leeches live in water.

As a rule, leeches are hermaphroditic and reproduce by depositing so-called cocoons, which are rounded bodies surrounded by a shell and containing eggs in an albuminous matrix.

While of very little medical importance in temperate climates, except for the fact that they were employed so extensively in therapeusis for blood letting of patients, they may be serious pests in many parts of the tropical world.

Hirudo medicinalis, *Limnatis nilotica* and *Haemadipsa zeylanica* are the species with which we are especially concerned.

Hirudo medicinalis is the species that has been used medically so extensively in earlier years for the extraction of blood. They have a secretion which prevents coagulation of the blood, so that when they are removed the wound still continues to bleed. These leeches are about 4 inches long and of a grayish-green color, with dingy red longitudinal stripes on the dorsal surface and with a dark-green ventral surface.

Limnatis nilotica is an aquatic species found in ponds, ditches, and other bodies of water in Northern Africa, Palestine and adjacent regions. The dorsal surface is greenish brown in color with orange-brown borders. The young leeches, which are only about 3 mm. long often gain access to the mouth when contaminated water is drunk. They have also been reported as entering the vagina and urethra in bathing in infected water. They attach themselves especially to the mucous membrane of the mouth, nose, larynx, or even trachea, remaining there several weeks, until they reach adult size (up to 10 cm. long and 1.2 cm. wide). They may cause headache and obstinate bleeding, often resulting in severe and even fatal anaemia. In some instances they have caused suffocation both by entering and occluding the air passages. Manson-Bahr has reported that they have thus caused suffocation, occasionally resulting in death.

A closely related species reported from the environs of Singapore is *L. maculosa*. Other related species have been found in Senegal and the Congo basin. Mazzola said he found in one instance an aquatic leech, *Haemopis cavillina*, fixed to the sclero corneal limbus.

Haemadipsa ceylanica, a related species, is a land leech found in India, the Philippines, Australia and South America. They are only about 1 inch (25 mm.) long and are slender. They leave the damp earth to climb shrubs and from there drop on animals or man passing through the forest. When the leeches are numerous, animals have sometimes been killed by the large amount of blood abstracted, and even human beings have been reported to have succumbed from the repeated small bleedings. Their bites are painless, but may be followed by ulcers. They also may get into the nostrils. They will even penetrate thick clothing in order to reach the skin.

Treatment

When fully engorged, the land leech, *Haemadipsa ceylanica*, drops off. Its removal may be hastened by touching it with a strong cocaine solution, which paralyses the leech and it quickly detaches itself. Removal may also be hastened by applying strong vinegar to the bite. The worm should not hastily be pulled off lest part of it, as the jaws, be left in the wound and a phagedaenic lesion develop. If the bleeding continues for some time, the flow of blood may be arrested with a styptic pencil.

In marching through jungle land, it is very advisable to protect the body from attack, as leeches can at times penetrate even rather thick clothing. Therefore the wearing of leather boots is advisable.

Since persons infested internally with *Limnatis nilotica* usually acquire it from drinking water, care should be taken only to drink water satisfactorily filtered or boiled.

The leeches lodged in the nasal passages, or in the pharynx may be located with a speculum and touched with strong cocaine solution, when they promptly detach themselves. If they are situated deeper in the posterior pharynx, larynx, trachea or bronchi, the patient should be placed in the Trendelenburg position before attempting to anaesthetize and remove them. Otherwise they may be drawn further into the respiratory tract and perhaps cause suffocation. Occasionally tracheotomy may be necessary to remove them. If they escape into the oesophagus and pass into the stomach, the parasite is rendered harmless by the gastric juice. For leech infestation of the genito-urinary tract, irrigations of strong salt solution have proved of value in removing and killing the leeches.

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Chapter XLVI

FILARIASIS, ONCHOCERCIASIS AND DRACONTIASIS

Definition.—Under the term filariasis there are included morbid conditions produced by certain parasitic nematodes of the superfamily FILARIOIDEA, the adults of which may live in the circulatory or lymphatic systems, the connective tissues, or serous cavities, while certain larval forms, often termed "microfilaria" commonly invade the circulating blood or the lymph spaces.

From a clinical standpoint, the term filariasis is in some respects unsatisfactory. Employed in its broadest sense, it obviously implies infestation of the host with any species of the superfamily and hence widely different pathologic conditions may be included under it. Hence special terms that will presently be discussed, have been introduced to indicate more clearly a number of the more important pathologic processes produced by the parasites.

Classification.—The five most important species of the superfamily FILARIOIDEA which infect man are:

(1) *Wuchereria bancrofti* (Cobbold, 1877) Seurat, 1921; Synonym, *Filaria bancrofti* Cobbold, 1877.

(2) *Loa loa* (Guyot) Castellani and Chalmers, 1913; Synonym, *Filaria loa* Guyot 1778.

(3) *Dipetalonema perstans* (Manson, 1891) Yorke and Maplestone, 1926; Synonym, *Acanthocheilonema perstans* Manson, 1891.

(4) *Onchocerca volvulus* (Leuckart, 1893) Railliet and Henry, 1910; Synonym or variation, *O. caecutiens* Brumpt 1919.

The guinea worm, *Drancunculus medinensis* (Linnaeus, 1758), Gallandat, 1773; Synonym: *Filaria medinensis* (Linnaeus, 1758), while a species of the superfamily or order FILARIOIDEA, is no longer classified in the family FILARIIDAE but in that of DRACUNCULIDAE Leiper, 1912 (Philometridae Baylis and Daubney, 1926). It is also of special clinical significance and the cause of important disease in man.

Infestation with these respective parasites is discussed under the following terms: (1) Filariasis due to *Wuchereria bancrofti;* (2) dipetalonemiasis; (3) loiasis; (4) onchocerciasis; (5) dracontiasis.

More than twenty species of filaria have been reported for man. However, at present a number of these are not recognized as valid. In addition to the species mentioned above, only *Mansonella ozzardi* (*Filaria ozzardi* (Manson, 1897), also known as *Filaria demarquayi* or *Filaria tucumana* (Biglieri and Araoz, 1917), *Dirofilaria magalhaesi* and *Dirofilaria repens* and *Loa inquirenda* (Maplestone 1938) are known to infect man.

Zoology.—The adult parasites of the superfamily or order FILARIOIDEA, Weinland 1858, Stiles 1907, are long, filiform nematodes in which the mouth is usually simple and without lips, occasionally bounded by chitinous structures or by small, insignificant lateral lips. The buccal cavity or vestibule is absent, or very rudimentary. The oesophagus is cylindrical and frequently divided into two parts, a muscular anterior and a glandular posterior part. The intestine is simple and sometimes atrophied posteriorly.

GENERAL FILARIAL TABLE

	Adults	Larvae	Remarks
Wuchereria bancroft (Filaria bancrofti).	Male 40 by 0.1 mm. Female averages 90 by 0.28 mm. Smooth cuticle. Bulbous anterior extremity. Occupy lymphatic glands and vessels.	Graceful curves; tail rather straight. Sheathed, up to 300 by 7.5 microns. Distance from head to V spot 90 microns; to break in cells 50 microns. Cells in head end form a curved line. Terminal cells do not fill up tail end. Nocturnal periodicity in peripheral circulation.	Transmitted by mosquitoes: *Culex: Aedes, Anopheles.* Causes elephantiasis, lymph scrotum, chyluria, etc.
Loa loa.	Male 30 by 0.3 mm. Female 55 by 0.4 mm. Cuticle tuberculated. Anterior extremity like truncated cone. Wanders in subcutaneous tissues.	Angular curves; acute bend at tail. Sheathed, 240 × 7 microns. Distance from head to V spot 65 microns; to break in cells 40 microns. Tail is completely filled up with terminal cells. Diurnal periodicity in peripheral circulation.	Transmitted by species of a biting fly —Chrysops. Causes Calabar swellings. Worms often visit ocular region.
Dipetalonema perstans.	Male 40 by 0.07 mm. Female 75 by 0.1 mm. Cuticle smooth. Anterior extremity club shaped. Tip of tail shows two triangular processes. Found about root of mesentery, and serous cavities.	Without sheaths, 200 by 5 microns. Posterior two-thirds tapers to blunt ending. Cells to end of tail. Distance from head to V spot 49 microns; to break in cells 34 microns. Persists in circulation both day and night.	Transmitted by midges: *Culicoides.* Pathogenicity questioned.
Mansonella ozzardi (Filaria ozzardi).	Female only is known; 65-80 mm. in length; a pair of fleshy papillae at tail end. Lives in retroperitoneal tissue.	Without sheaths, 200 × 5μ. Tail sharp pointed; cells not to end of tail.	Transmitted by midges: *Culicoides furens.* No pathogenicity.
Onchocerca volvulus. (O. caecutiens).	Males 18-30 by 0.15 mm. Females usually fragmented, 35-50 cm. by 0.4 m. Cuticle striated. Found coiled up in cyst-like tumors under the skin.	Without sheaths. 250 by 7.5μ. Found in cyst-like spaces in nodules and in cutaneous lymph spaces.	Transmitted by flies of genus *Simulium.* Causes small subcutaneous cystic tumors, skin eruptions, punctate keratitis, blindness.
Dracunculus medinensis.	Male from dog infected by Moorthy 2.4 cm. Female 80 to 90 cm. long by 1.6 mm. wide. Smooth white body. Anchoring hook at tail end. Female often lives in subcutaneous tissue of lower extremity.	Without sheaths. 600 × 20 microns. Tapering outline; gut present. Long slender tail. Cuticle striated. Extruded from break in skin of patient. Not present in blood or tissues.	Larvae develop in *Cyclops.* Man infected by drinking water containing *Cyclops.* Causes "Dracontiasis."

In 1936 Nolasco and Africa reported a case of overwhelming internal infection of the body of a patient with filariform larvae of *Strongyloides* associated with and presumably due to paralytic ileus.

In 1938 Torres and Azevebo reported autopsies upon 2 cases in which they found rhabditoid larvae alone migrating from ulcers of the mucosa of the colon by way of the

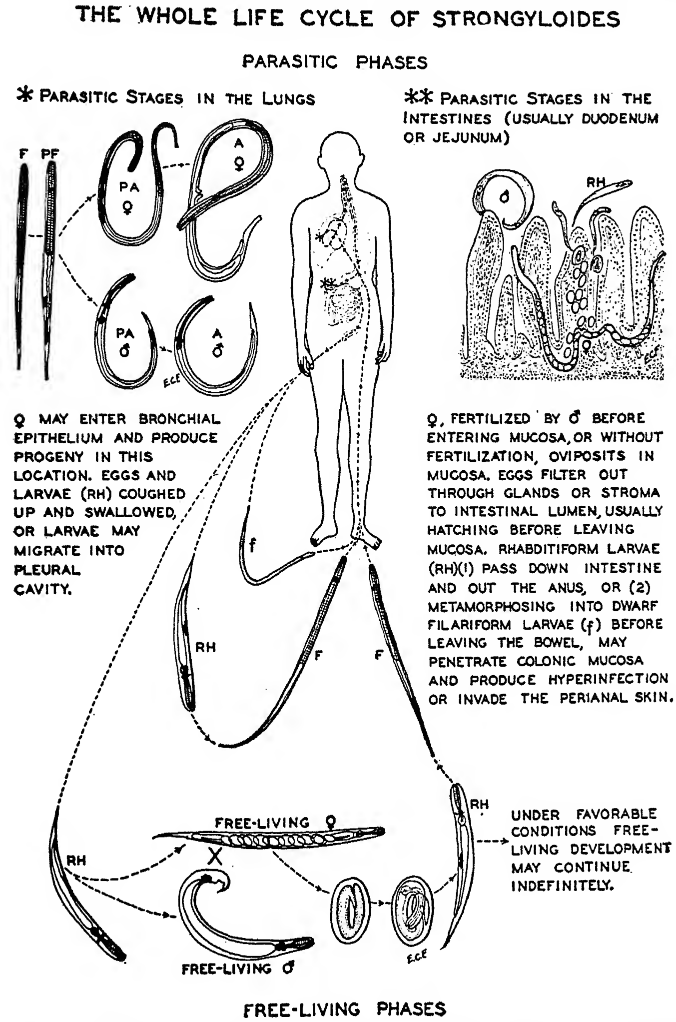

FIG. 288.—Diagrammatic representation of the whole life cycle of *Strongyloides*. (After Faust. Rev. de parasitol., Habana.)

subserous lymphatics of the mesocolic lymphatics to the colic veins and thence to the liver and lungs. They believe that this indicated a direct developmental cycle of internal auto-infection or hyper-infection.

Finally, Faust and deGroat (1940), in a study of a case of infection in a male child, found in a microscopic study of some of the tissues from the

intestinal wall, mesenteric lymph nodes and liver, taken at autopsy, various stages of development and invasion by the parasite. It therefore seemed obvious that self infection in strongyloidiasis may result both from perianal infection of the skin and from the penetration of larvae directly through the bowel wall.

Infection of man may take place by direct ingestion of the larvae which then penetrate the mucous membranes, or the larvae may penetrate directly through the skin. They then pass through the blood stream to the lungs where they remain for some days, developing according to Faust into adolescent males and females. Here they cause more or less acute inflammation, as do *Ascaris* larvae. Filariform larvae have rarely been found in the sputum.

According to Faust insemination occurs chiefly in the lungs. Some worms start reproduction in the lungs. Most of the parasites pass by way of the trachea and the oesophagus into the intestine, where the female bores into the mucosa and begins to deposit ova about two weeks after penetration of the skin. The parasitic males, which are only 0.5 to 0.8 mm. long and resemble the free-living males, do not penetrate the mucosa and are quickly eliminated. After the supply of spermatozoa is exhausted the female continues for a time to form ova parthenogenetically.

If the perineum is left soiled with infected faeces, development may take place in situ, and the filariform larvae penetrate the skin, superinfecting the host. They may produce local itching urticarial lesions, a manifestation of hypersensitiveness to strongyloid protein. Fülleborn has shown that local allergic reactions may be obtained by cutaneous application of extracts of dried larvae.

Epidemiology.—In the analysis of 85 cases of *Strongyloides* infection in Louisiana, Hinman found a marked preponderance in males, 59 to 26. According to age, the highest incidence occurred in the 13–19 year group. Although 47 per cent were under 20 years old, the third and fourth decades showed a considerable number of cases. Faust (1931) found the highest incidence in Panama in the 11–15 year group, after which it remained generally constant.

An analysis of occupation has shown that in Louisiana about one-third are school children, and almost half were farmers, housewives, or common laborers, the groups which might be expected to be exposed to infection most frequently. Also, in Louisiana the disease was more common in whites than in the colored race. Fulleborn has also pointed out that clinical symptoms are much more rarely present in negroes and other natives than in white people.

Experimental infection with *Strongyloides* as noted can occur either through the oral or intestinal mucosa, but it is usually regarded that in nature, soil contamination of the skin is the usual route of infection. However, it seems evident that contaminated food or water may occasionally be a factor (DeLangen, 1936; Blacklock, 1938).

The free-living generation shows comparatively little resistance in the soil and the worms are unable to survive for any length of time in water. Nevertheless, the free living stages have been believed generally to serve as an adaptation for the preservation of the species. Beach (1935) has shown that on suitable culture medium the free-living cycle may be carried on through possibly 3 generations experimentally. Whether or not such multiplication occurs under natural conditions remains to be determined. Dogs have been found naturally infected with a species of Strongyloides morphologically and physiologically indistinguishable from that which occurs in man. Galliard (1940), in Tonkin, has found that young dogs are easily infected with the human *Strongyloides*. In heavy infections, larvae are found in the stools on the seventh day. The animal always dies on the tenth or twelfth day. Monkeys may also be experimentally infected with the human parasite. The infective stage larvae of these animals, like the human species, are developed in the soil, from which man may become infected through skin contact, as in hookworm infection.

connection with the history of the disease, demonstrating that the mosquito, *Culex fatigans*, subserves the parasite as an intermediate host.

At first Manson thought that the fully developed microfilariae escaped from the body of the infected mosquito into the water at the time of the death of the insect, and that man contracted the infection by drinking such water. Later Low, in 1899–1900, discovered that the larvae undergo further development and eventually pass into the proboscis and labium of the insect. Grassi and Noe soon confirmed these experiments with *Dirofilaria immitis* and produced infection in dogs through the bites of other infected mosquitoes (*Anopheles maculipennis*). Fulleborn, Manson-Bahr and others have likewise proved that the larvae escape by way of the mosquito's proboscis and enter the skin of their definitive host.

Manson, in 1880, also described a remarkable phenomena known as *filarial periodicity*, relating to the time of the appearance and disappearance of the microfilariae in the capillaries of the skin and superficial blood vessel. He also proposed to call the larval form of the filaria, in order to emphasize its nocturnal periodicity, *Filaria nocturna*. Owing to the rules governing zoological nomenclature, it became necessary to discard such earlier appellations, though the name of *Microfilaria bancrofti* is still commonly applied to the larval stage which is encountered in the blood.

Geographical Distribution.—*Wuchereria bancrofti* has the most extensive geographical distribution of all the Filariidae and occurs in practically all warm countries. It has been found in the western hemisphere from Charleston, S. C., as far south as the Argentine in South America and in the eastern hemisphere from southern Spain, particularly Barcelona, as far south as Brisbane in Australia. It is especially prevalent in India and South China, extending as far north as Shantung Province and southern Japan and southwardly to the Dutch East Indies and other islands of the Pacific where, in some localities, 80 per cent of the inhabitants are known to be infected. Hargrave reported that filariasis in American Samoa probably causes greater damage than any other disease by reason of the disabling effect and the undermining of the general health which may predispose to other infections. Phelps, in American Samoa, reported filariasis as the third cause of death in frequency, the first cause being tuberculosis and the second pneumonia. A survey of the native guard and civil employees there showed 48 per cent harboring microfilariae in the blood. However, the rate of filariasis frequently varies in adjoining areas in the Pacific islands, as has been especially demonstrated by Manson-Bahr. In the present war numerous cases have occurred among our troops in the Pacific Islands. (See page 1326.)

The infection is also common in Arabia and West and Central Africa. In South America it is common, especially along the northern coast, but apparently it has not extended far inland in the Guianas, Colombia and Panama, where *Mansonella ozzardi* has recently been found more prevalent. It is common in the greater and lesser Antilles. In the United States, Charleston was formerly an endemic focus of infection. Observations upon the occurrence of the infection at Charleston or Mobile in earlier years was made by John Guiterras, de Sausure, Mastin and others, and in 1913 Matas reported upon the occurrence and treatment of elephantiasis in New Orleans. In 1915, Johnson found that 19 per cent of the patients admitted to the Roper Hospital in Charleston harbored *Microfilariae* in their blood, and in 1919 Francis, of the United States Public Health Service, found among 400 individuals living in Charleston that

77 were infected with *Microfilariae bancrofti*. He also detected a few cases of the disease elsewhere in South Carolina and in Jacksonville and Tampa, Florida. The latter cases, however, had previously lived at some time either in Charleston or in Cuba. Sporadic cases of infection appear from time to time in different parts of the United States, particularly in the larger cities, the primary infection probably having occurred in subtropical or tropical countries. Poindexter and Jones (1934) have reported a case supposed to have originated as far porth as Washington, D. C. It is not now endemic anywhere in the United States.

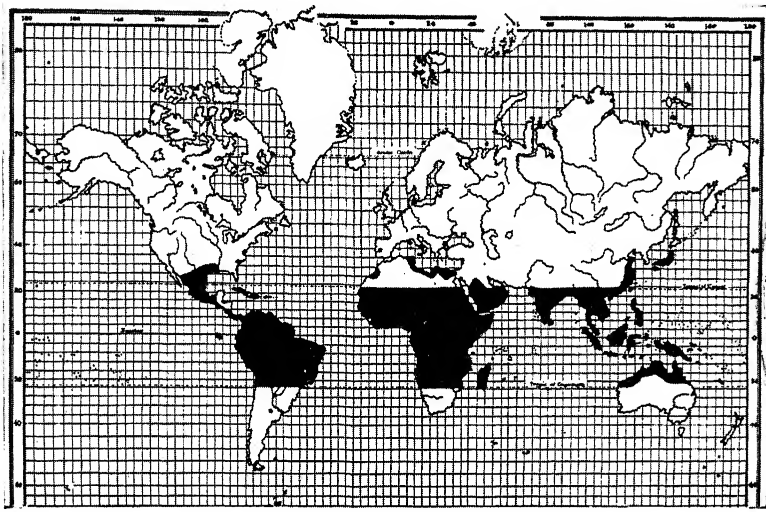

FIG. 291.—General distribution of Filariasis.

Etiology.—The *adult parasites* of the species *Wuchereria bancrofti* are threadlike, white and translucent in appearance, with a smooth cuticulum. Although tapering towards both ends, their terminals are bluntly rounded. The head is slightly bulbous, and is provided with two rows of small sessile papillae. The mouth is without lips and is unarmed. The oesophagus has no distinct bulb-like swelling at the posterior extremity. The males measure from 40 to 45 mm. in length, by about 0.1 mm. in breadth. The caudal extremity is curved sharply ventrad. Leiper and Faust have distinguished twelve pairs of sessile caudal papillae of which eight pairs are preanal and four immediately postanal in position. Further caudad there are two pairs of rather large, sessile papillae, and at the caudal extremity a solitary pair of minute size. Caudal alae are often indistinct. The two copulatory spicules are of unequal length, the longer one being cylindrical and tapering to a long lash, the shorter one being trough-shaped. The females measure from 65 to 100 mm. in length, with a breadth of from 0.24 to 0.3 mm. The vulva is situated about 0.6 mm. to 1.3 mm. from the cephalic end. The uterus, which occupies the greater extent of the body, contains the ova, which measures about 40μ in length by 25μ in breadth; in the anterior portion of the uterus well-formed embryos are often contained. The ova are enveloped by a transparent membrane, apparently chorionic in origin, which gradually becomes stretched out and adapts itself to the length of the embryo as it straightens itself, and which constitutes what is known as the sheath of the microfilariae after its exit from the parent worm. This sheath is frequently somewhat longer than the enclosed microfilariae, and the

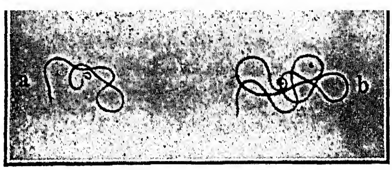

FIG. 292.—Male (a) and female (b) of *Wuchereria bancrofti*. Natural size.

organism is thus able to move back and forth within it. While most zoologists believe that the sheath is a modified vitelline membrane, Augustine (1937), from the study of another species of *Vagrifilaria* which occurs in ground doves, believes that the sheath is merely the result of an incomplete ecdysis. In other species of the *Filariidae*, such as *Dipetalonema perstans*, the larvae hatch or escape from their sheaths while still within the uterus of the adult female, which is thus viviparous.

Microfilaria.—The fully mature female gives birth to an enormous number of the larval forms or microfilariae. These, after leaving the parent worm, either remain in the lymph or migrate by the lymph vessels to the blood stream. When seen in fresh preparations of the peripheral blood or lymph, or in chylous urine, they have a very lively motility. They measure from 125 to 320μ in length by 7 to 10μ in breadth.

The cuticula is smooth, the head is round and at the anterior extremity a protrusible, minute refractile rod or stylet can sometimes be seen. On vital staining, or in fixed preparations stained with hematoxylin or Giemsa's solution, the sheath, as well as the inner structure of the organism, can be more clearly differentiated. Four equidistant papillae on the oral end have been noted by Abe. The tail is distinctly pointed. The body of the larva is composed largely of small subcuticular cells. The central axis consists of a column of cells with deeply-staining nuclei. Interruptions in the staining, and the position of these cells, are interpreted to indicate the location of certain "anlage" of the worm. They relate particularly to a first break in the column of cells, about 20 per cent of the length of the organism backward from the anterior extremity, perhaps indicating the nerve ring; to a second hyaline V-shaped space about 30 per cent from the anterior end, representing the undeveloped excretory pore, and adjacent to it an excretory cell; and third, to a somewhat similar but smaller spot a short distance from the end of the posterior extremity which has been termed the tail spot, and which probably represents the incipient anus or cloaca. Four genital cells can also frequently be distinguished in the posterior portion of the organism, three being situated close together in front of the anal pore, and the fourth and largest about 70 per cent of the length of the larva from the anterior extremity. The relative position and distances of these structures or "anlage" from one another, together with the size and relation of length to breadth, are somewhat constant for the species and are utilized for the differentiation. Thus, in *Wuchereria bancrofti* the terminal 5 per cent of the larval form is free from the rod-like nuclei, which serves to distinguish it from the larval forms of *Dipetalonema* and *Loa* in which the nuclei extend further to the tip of the caudal extremity. Also, what is known as the "Innerkörper" of Fülleborn, consisting of a red-staining mass in which may be distinguished a series of discrete nuclei on a blue background extending for one-tenth the length of the worm, distinguish it from *Microfilaria loa*. Fulleborn and Rodenwaldt give the following location of these structures, of value in diagnosis in *Microfilaria bancrofti:* nerve ring, 20 per cent distance from the anterior extremity; excretory pore, 29.6 per cent; excretory cell, 30.6 per cent; genital cell No. 1, 70.6 per cent; anal pore, 82.4 per cent; genital cells Nos. 2, 3 and 4, situated immediately in front of the anal pore.

There has been no true cultivation of microfilariae in vitro, though they have sometimes been kept alive, for example, in defibrinated blood in test tubes for as long as six weeks, but with no definite development.

Filarial Periodicity.—A striking phenomenon, first noted by Manson in 1880, regarding the time of the appearance and disappearance of the *microfilariae* in the capillaries of the skin and superficial blood vessels, is referred to as filarial periodicity. In explanation of this it has been suggested that in some species of Filariidae there is more or less definite adaptation between the habits of the microfilariae and those of the insect

Treatment

Chopra and Chandler have pointed out the difficulties in the treatment. Since the parasites penetrate inside the mucous membrane, a satisfactory drug would have to be fairly absorbable.

They found that oil of chenopodium has practically no favorable effect and that the parasites persist even after many courses of treatment. Carbon tetrachloride likewise has little or no favorable action. DeLangen (1936) has employed gentian violet by mouth, combined with intravenous use of tartar emetic. Faust (1940) recommends medicinal gentian violet. He suggests for the average case the dye be administered before meals in enteric coated tablets, 1 grain (0.06 gm.) 3 times daily until 50 grains (3.3 gms.) have been taken. The dosage is the same for children as for adults. For refractory cases 25 cc. of a 1 per cent aqueous solution of the dye may be intubated into the duodenum with good results. In human cases of strongyloidiasis, the success of treatment with enteric-coated tablets or by intubation of the solution has been attested by many physicians in the United States, and in tropical America by Ceballos Carrion (1934) and Kouri, Sellek, and Rivera (1936). For pulmonary infection and for severe late-stage intestinal cases he advises the dye should be introduced intravenously in 0.5 per cent aqueous solution in amounts not in excess of 25 cc. on alternate days for a period not in excess of 10 days. Gentian violet is slightly irritating to the intestinal mucosa and has a mild stimulating effect on the heart. For intravenous use the above instructions must be exactly followed to prevent precipitation of the dye within the blood stream. For such therapy the patient must be hospitalized and should be given personal supervision during and following the injection.

Brown (1934) points out that patients to whom gentian violet is administered should be watched carefully for any signs of toxicity such as loss of appetite, nausea, vomiting, weight loss, and the drug temporarily discontinued if they occur.

Hinman employed gentian violet therapy in 46 of his 85 cases. None of the patients were subsequently readmitted to the hospital for treatment and there was no mortality in the series, but subsequent stool examination to check the value of the treatment was not made in a large number of cases.

Simpson (1939) has suggested compound solution of iodine (U.S.P.) introduced into the duodenum through a transduodenal tube. The dose finally fixed was 60 minims (4 cc.) given on alternate days until neither the duodenal contents or faeces showed ova or parasites. He reports 9 cases successfully treated by this method.

Prevention

The prevention should consist in measures which are known to be of value against hook worm disease, especially the proper disinfection and disposal of faeces, the wearing of shoes, and avoiding contact with soil which may be contaminated. Also it should be borne in mind that infection might occur from drinking water in marshy districts, and from uncooked vegetables fertilized by infected excrement. Strongyloid larvae have been found on the leaves of vegetables, as well as in contaminated drinking water.

Rare or Spurious Nematodal Infections

Capillaria hepatica, Bancroft, 1893. (*Hepaticola hepatica*, Bancroft, 1893).—Among other Trichuridae is *Capilaria hepatica*, a very common parasite of the liver of rats and other rodents and the chimpanzee and some monkeys, less commonly the dog. The eggs resemble those of *Trichuris*, but have an outer shell, a pitted surface, and measure 51 to 67.5μ by 30 to 35μ (Faust). They accumulate in the liver and form dry, yellow mottlings. The eggs remain in the liver and after the death of the host they may be freed by decomposition. Infection may occur by the ova being transmitted by

flies to food, or by the eating of the infected liver. Only one valid human case has been reported, from a British soldier in India, but some 30 cases of temporary or pseudo-infection have been published, in which the ova were presumably eaten with livers of infected animals in Panama, French Guiana, Southern Rhodesia, and Russia [Faust (1931), Vogel (1932), Sandground (1933)]. Foster and Johnson (1939) refer to the probable origin of the cases in man in Panama. They found the white-lipped peccary *Tayassus pecari spiradens*, the red spider monkey *Ateles geaffroyi*, and the white-faced monkey *Cebus capucinus imitator* all infected. Some Panamanians eat all of these animals. On feeding boiled infected livers to other healthy monkeys, Foster found infection resulted.

Thominx aerophilus, of the family Trichocephalidae, usually found in the trachea, lungs and nasal cavity of carnivorous animals (cats, dogs, wolves, foxes, etc.), in Europe and the United States, has been reported by Skirbin (1939). The author reports its occurrence as a facultative parasite in a patient in Moscow in a hospital, suffering from severe tracheo-bronchitis. The eggs of the nematode were found in freshly expectorated sputum, while the faeces of the patient contained, in addition, the eggs of *Trichuris trichiura*.

Other Spurious Infections.—Species of Mermithidae (the so-called cabbage snakes) have been reported in man in a few instances, but they produce no symptoms and hence are of no clinical importance. Reports of a coprophilous nematode, *Rhabditis hominis*, contaminating the stools after defecation, have sometimes been made. Thus Sandground reported that a large proportion of human *Strongyloides stercoralis* infection, formerly diagnosed as such in the clinical laboratories in the State of Georgia, U. S. A., were in reality cases of pseudoparasitism with this nematode.

Chandler (1938–1940) has found *Diploscapter coronata* in the aspirated stomach contents of 9 patients in Texas, in which there was almost complete lack of hydrochloric acid. This parasite has previously been known only as an inhabitant of soil or sewage beds. A related species is parasitic on living roots of plants. These worms also had been previously incorrectly diagnosed as *Strongyloides*.

The vinegar eel, *Turbatrix aceti*, has been found on several occasions in the urine or in vaginal exudates of women who had accidentally introduced the parasites into the vagina in using vinegar as a vaginal douche.

A few instances of infection of man with nematodal parasites of plants have been recorded. On one occasion, *Anguillulina putrefaciens*, a common parasite of onion bulbs, was observed in the vomitus of a patient who had eaten uncooked onions. *Heterodera radicicola* commonly infects the roots and stems of many edible plants and when they are consumed by man the ova and larvae have at times been observed in the faeces. Kofoid and White found the ova of this species and attributed them to an unknown intestinal parasite of man "*Oxyuris incognita.*" *Heterodera radicicola* is obviously not a true human parasite. Keller (1935) points out, however, that the ova may be confused with unfertilized *Ascaris* or with hookworm ova and hence may result in unnecessary treatment. The ova are thin shelled, hyaline, elongated, ovoidal in shape, with rounded ends. Sometimes they are slightly flattened on one side. They measure from 80–120μ by 25–40μ and in some instances contain fully developed larvae.

Other Helminthic Infections

SPIRUROIDEA

Members of this superfamily may be plump, resembling *Ascaris*, or long and filiform, resembling *Filaria*. Lips when present, 2, paired, simple or trilobate chitinous buccal cavity. Oesophagus practically always divided tandem. Vulva more equatorial. Family of interest: SPIRURIDAE.

Spiruridae

Physalopteriasis.—*Physaloptera caucasica* (Linstow, 1902) Syn. *P. mordens*, Leiper, 1907 is normally a parasite of monkeys and has been reported in man in eastern and

Although much work has been done upon the subject, both in earlier and in recent years, the periodicity of filaria has never been satisfactorily explained. Among many theories, the following have been especially advanced in recent years:

1. That it depends in some way on the hours of rest, sleep and activity, since the periodicity may be reversed by changing the habits of the infected individual.

2. That it is related to the habits of the insect host of the larvae, the insect host that transmits the infection.

3. Clayton Lane, especially, believes it depends upon a daily cyclical parturition of the female filaria with the daily destruction of all the microfilariae. He believes all of the microfilariae are born at a regular hour each day and, after a certain interval, reach the peripheral circulation. In his recent articles on the subject he states that the daily destruction of microfilariae is accomplished by the reticulo-endothelial system.

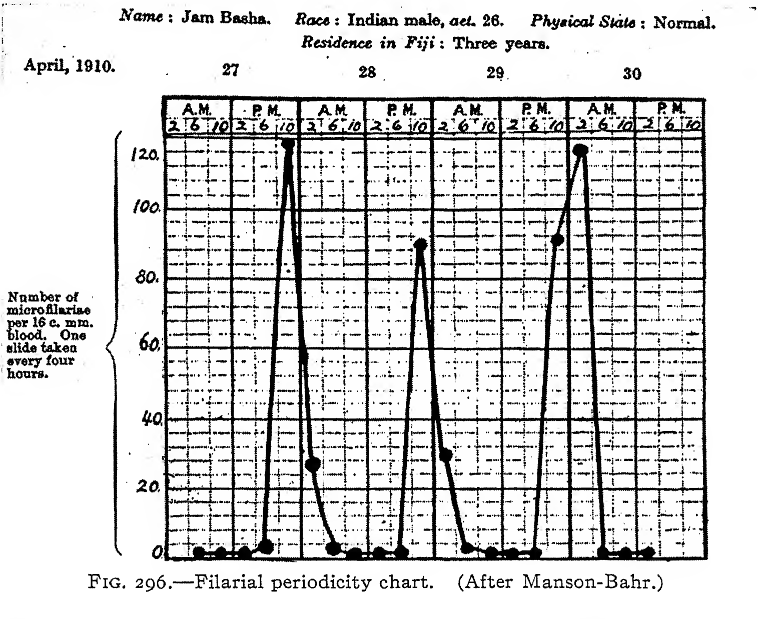

FIG. 296.—Filarial periodicity chart. (After Manson-Bahr.)

O'Connor demonstrated that in some instances by the examination of serial sections of adult female worms, removed surgically from patients in New York City, the uterus at a certain period of the day was completely filled with embryos, whereas at another period the uterus was empty and collapsed. O'Connor and Hulse (1932) thought that the microfilariae were born at about mid-day and that some time was spent in their filtering through the lymphatics, so that they probably would begin to increase in numbers in the peripheral circulation in the evening. However, in a subsequent report found among the papers of the late Dr. O'Connor and published after his death (June, 1938) he wrote that while there was evidence from his former work, performed with Hulse, that parturition occurs about noon, from his last case in which filarial tissue was removed by operation he felt "that parturition always occurs about noon is not upheld by the present evidence, although it seems to have been imminent at the time of operation." The operation was performed at 2.45 p.m. However, even if parturition always occurred about noon such a condition would only explain filarial periodicity, provided that a comparable destruction of the microfilariae occurred shortly after midnight and, second, that the female worms are capable of producing each day such an

enormous number of microfilariae. There is no scientific evidence yet that such destruction and rebirth occurs.

Hinman (1935) has demonstrated that in dogs, where the question can be studied more accurately and extensively, cyclical parturition does not occur with *Dirofilaria immitis*. Regardless of the time of day of the examination, the adult worms were always found to contain many active microfilariae. He also produces evidence to show that it seems highly improbable that the adult parasites could produce daily the number of microfilariae found in the blood.

There is much evidence, also, to show that microfilariae live for considerably longer than twenty-four hours in the circulating blood. Rao (1933) has found that microfilariae survived *in vitro* for 4 to 6 weeks under aseptic conditions, while Hinman (1935) found that microfilariae of *Dirofilaria immitis* maintained their activity in incubators at 39°C. for 10 days in citrated blood.

Underwood and Harwood (1939) transfused intravenously an uninfected dog with blood containing approximately 233,000 microfilariae of *Dirofilaria immitis*. Some, but comparatively few of the microfilariae appeared in the peripheral circulation following injection. However, these survived in the blood stream of this dog for more than 2 years, though no increase in size of the embryos was noted at any time. At autopsy of the animal, about two and one-half years after the injection of microfilariae, no embryos could longer be found in the blood.

Rao (1933) reported 2 cases with filarial cysts, in which the adult filariae were removed with the cysts by operation; in one, the microfilariae disappeared completely between the second and third month after the cyst was excised; in the other, 70 days after the removal of the cyst and adults. In these cases there was apparently no sudden or large daily mortality of the microfilariae.

Knott has reported a series of transfusions of human blood containing the microfilariae of *Wuchereria bancrofti* into non-infected humans. After a number of failures, he states one transfusion resulted in viability of microfilariae for 14 days and the observation of typical nocturnal periodicity of these transfused embryos. This patient had received 175 cc. of blood, containing 4,000 microfilariae per cc., a total of some 700,000 microfilariae. The writer, and also Hinman (1937) thought this evidence very conclusive that the microfilariae lived for at least 14 days. Gonnert reports that he injected himself intravenously with 160 cc. of blood from a patient infected with *Loa loa* and *Acanthocheilonema perstans*. While most of the *mf. loa* disappeared from the blood in the first few days, some of the *mf. perstans* persisted for as long as 3 years. The author had never visited any region with endemic filariasis and so the possibility of latent infection could be excluded.

Hinman (1937), moreover has continued observations of adult *Dirofilaria* in artificial media in vitro, consisting of blood serum diluted with saline and Ringer's solution, and has found no evidence whatever of cyclical parturition, but only that there is a more or less continuous parturition being carried on. Hinman, Faust and de Bakey (1934) also transferred infected blood into a non-infected dog. Active microfilariae were found in the recipient's blood for a period of over six weeks.

Harley (1932) suggested that there was a chemiotactic substance in the saliva of insects which produced a stimulus for cyclical parturition. However, Hinman has been unable to isolate any such substance from several species of mosquitoes, though O'Connor showed *Culex fatigans* could abstract many more microfilariae from the blood than *Aëdes aegypti*. Khalil (1938) believes that the site of the adult filaria in the human body may be a determining factor as to whether the microfilaria is periodic or nonperiodic. However, this has not been demonstrated and obviously the mechanism of filarial periodicity is still unsolved.

Transmission.—With all the microfilariae, an intermediate host is necessary for the further development of the parasite, and with the exception of *Dracunculus medinensis*, the intermediate host is an insect. When the appropriate insect host sucks blood from an infected individual, the microfilariae pass into the stomach of the insect together with the blood

meal. In the case of *Mf. bancrofti*, the embryos, after arriving in the stomach of the insect, if they are still within the sheath, escape from

FIG. 297.—Section of *Aëdes pseudoscutellaris*, showing filariae in thorax on tenth day of development, traveling forwards into proboscis. (By permission from Manson's Tropical Diseases.)

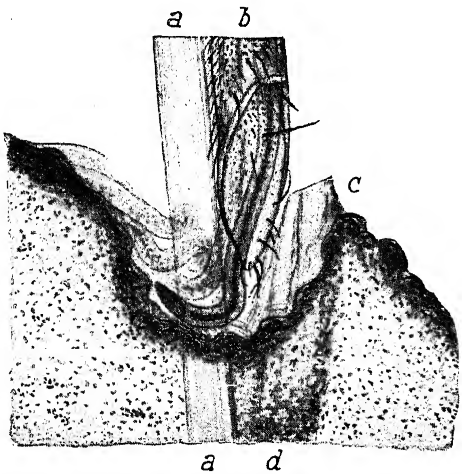

FIG. 298.—Filaria emerging from the end of a mosquitoe's proboscis upon the skin × 250. Semi-schematic. (After Fülleborn.)

the sheath within a few hours after ingestion. Within 24 to 48 hours they have migrated through the gut wall to the thoracic muscles of the

insect, where they soon change considerably in form, becoming shorter and stouter and more sausage-shaped, but with a sharp, tail-like process.

They now have lost greatly their active motility and finally become quiescent. In the further development, one or more moults (shedding of cuticle) take place and in the course of a week considerable changes occur in their internal anatomy, the gut, rectum, anus and body cavity having become differentiated. During the course of another few days the larvae increase considerably in size, becoming more slender and elongated, and again take on even more active motility. Still later they begin to migrate from the thoracic muscles, chiefly in the direction of the head though some of them pass into the abdomen, particularly in the malpighian tubes and in the fat body, and even into the legs of the insects, and undergo development there. Many of them penetrate into the muscular labium of the proboscis. The final infective stage of the filariae, measuring from about 1 to 2 mm. in length and about 20μ wide, may be found in the proboscis, usually in from 12 to 24 days after the insect has imbibed infected blood. Depending particularly upon the temperature and moisture, or perhaps to some extent upon the species of insect, the complete period of development in the insect may take from 10 days to 6 weeks.

When the insect again feeds on human blood, the microfilariae, sometimes several at a time, moving downward through the labium, break through Dutton's membrane when it is put upon a stretch by the wide separation of the labella at the time of the feeding of the mosquito. Arriving on the surface of the skin of the human host at or near the point of puncture, they then penetrate the skin and reach some part of the lymphatic system, where the potential males and females are believed to grow to sexual maturity. The females become fertilized by the males and new generations of microfilariae later reach the blood stream of the host. Eventually some of the adult parasites give rise to the different pathologic conditions. It is not known how long it takes for the larvae to become mature, but it is probably many months before the female begins to give birth to microfilariae.*

It should be noted that there is no multiplication of the larvae in the insect. The larvae taken in at the time of feeding of the insect merely grow and become transformed into the infective stage in the mosquito.

The complete development of the larval forms of *Wuchereria bancrofti* has been observed in the following mosquitoes:

1. *Aëdes aegypti:* West Africa, New South Wales, Dutch Guiana
2. *Aëdes* (*Finlaya*) *togoi:* Japan
3.† *Aëdes variegatus* (*Stegomyia scutellaris*)*:* Samoan and Fiji Islands.
4. *Aëdes ochraceus:*[1] Nigeria
5. *Anopheles* (*Nyssorhynchus*) *albimanus:* Caribbean
6. *Anopheles albitarsus:* Brazil
7. *Anopheles* (*Anopheles*) *algeriensis:*[2] Tunis
8. *Anopheles barbirostris:* India
9. *Anopheles* (*Myzomyia*) *gambiae* (*A. costalis*)*:* West Africa
10. *Anopheles fuliginosus:* India
11. *Anopheles funestus:* West Africa (Sierra Leone), 1932
12. *Anopheles hyrcanus* var. *nigerrimus:* India

[1] *One instance reported by A. W. Taylor in Nigeria* (1930).

[2] *Reported by error, according to Senevet.*

* Some suggest from 9–12 months. In some instances sections of the glands have revealed immature parasites in individuals who have resided less than 6 months in the endemic area.

† Synonym *Aedes scutellaris* var. *pseudo-scutellaris.*

13. *Anopheles hyrcanus* var. *sinensis:* China, Japan
14. *Anopheles ludlowii* var. *sundaica:* India
15. *Anopheles* (*Myzorhynchus*) *nigerrimus:* Travancore
16. *Anopheles pallidus:* India
17. *Anopheles philippinensis:* India
18. *Anopheles pseudojamesi:* India
19. *Anopheles punctulatus:* New Guinea
20. *Anopheles rhodesiensis:*[1] West Africa (Sierra Leone), 1932
21. *Anopheles* (*Mzomyia*) *rossi* (*A. subpictus*): India
22. *Anopheles squamosus:*[2] West Africa (Sierra Leone), 1932
23. *Anopheles stephensi:* India
24. *Anopheles amictus:* Queensland
25. *Anopheles varuna:* India
26. *Culex fatigans* (*C. quinquefasciatus*): China, India, Egypt, Australia, West Indies, Antilles, Trinidad, Philippines, Pacific Islands, St. Lucia, and Charleston, South Carolina
27. *Culex pipiens* (*C. pallens*): Central China, Japan, Egypt (Cairo) 1933
28. *Culex vishnui:* India
29. *Mansonia* (*Mansonioides*) *pseudotitillans:* Malaysia
30. *Mansonia* (*Mansonioides*) *uniformis* (seu *africanus*): Central Africa
31. *Mansonia* (*Mansonioides*) *annulifera:* India
32. *Mansonia* (*Mansonioides*) *juxta:* Brazil

Undoubtedly other species may be found to be appropriate hosts as other investigations are made. However, experimental demonstrations in the laboratory do not necessarily indicate that all of the species of mosquitoes in which the larvae have completely developed constitute common intermediate hosts. *C. fatigans*, *C. pipiens*, *A. variegatus* and *A. rossi* and *costalis* are particularly common transmitters. Yao (1938) reports that *Microfilariae bancrofti* may also develop in the sandfly *Phlebotomus sergenti* (var. *mongolensis*).

Knight (1944) has summarized our present knowledge in regard to the transmission of the infection in the South Pacific and Australia as follows: Filariasis appears to be predominantly nocturnal from South Queensland through New Guinea to the Solomons and New Hebrides. The chief vector of the nocturnal form in Australia is the night-biting, domestic and widely-spread *Culex quinquefasciatus* (= *Culex fatigans*). In New Guinea, there is undoubtedly another vector for the regions outside the few areas of permanent white settlement. The anophelines may well be the most important vectors in those areas for *Anopheles punctulatus* (subspecies not specified) has been found naturally infected with filaria in New Guinea by Backhouse and Heydon. In addition, Heydon obtained artificial infection in *Anopheles amictus*. In the Solomons and New Hebrides epidemiological evidence would indicate that *Anopheles punctulatus farauti* (= *A. p. moluccensis*) is the vector.

In the Fijis and in Polynesia, filariasis is relatively non-periodic with the tendency being towards a diurnal strain. Here the vector is a day-biting mosquito, *Aedes scutellaris pseudo-scutellaris*, which breeds in all types of natural and artificial water-holding containers such as halved coconut shells, tree holes, tin cans, rain-barrels, etc.

PATHOLOGY

In many instances in which the presence of the adult filarial parasites in the body is recognized by the occurrence of microfilariae in the blood, the parasites exercise no recognizable injurious influences or pathologic changes. On the other hand, in many cases grave lesions result. Some authorities who have a very wide experience with filariasis say that in many or most cases the parasite exercises no manifest injurious influence whatsoever (Manson, 1928). However, O'Connor and Hulse, (1932), have shown that in some persons who have never complained of symptoms and are unaware of any disturbance, marked pathologic changes associated with filarial infection may occur. Various stages of inflammatory reaction and fibrosis were found by these authors about adult filariae in the lymphatic glands removed by operation from a patient who had no prior knowledge of the local condition.

Undoubtedly in many cases with microfilariae in the blood, no manifestation of disease may be noted for long periods, as Low has pointed out. However, it seems pos-

[1] *Allowed complete development, but no record of its infection in nature.*

[2] *Uncommon in Sierra Leone and hence unimportant as a host.*

sible if a large series of cases were carefully followed-up for a period of years that some of them would develop symptoms of some sort and anyone who reveals the presence of infection is potentially liable to attacks of filarial disease. The number and location of the parasites and whether they are alive or dead may also influence the clinical manifestations of the disease. In many cases of infestation in which there are no unfavorable symptoms, the presence of eosinophilia, which may be moderate or pronounced, and is common in certain other helminthic infections, demonstrates a probable toxic effect of the parasites. It is now well recognized that patients with elephantiasis of filarial origin may fail to show microfilariae in their blood. Hence the absence of microfilariae in a case of elephantiasis in no way justifies the opinion that the elephantiasis is not filarial in origin. As a result of lymphangitis, lymph stasis, and blocking of the lymph channels, the lymphatics draining the affected area may be so effectively obstructed by the parasite or the products of inflammation about it that the microfilariae may be prevented from reaching the peripheral circulation. Sometimes operation upon an enlarged fibrotic lymphatic gland or a group of such glands may open up new channels of circulation from the mature female and may lead to the appearance of microfilariae in the blood which had not previously been observed there. Manson-Bahr notes that adult filariae of both sexes in large numbers have been found in enlarged fibrosed lymph glands, the epitrochlear for example, without the presence of the corresponding microfilariae in the blood stream. In many instances also the adult parasites may have died, particularly during attacks of lymphangitis.

The pathologic processes due to filariae which produce clinical manifestations are obstruction of the lymphatic channels of a progressive nature and inflammatory conditions associated with fever. Bacterial infections due to streptococci or staphylococci also frequently play an important role in the production of some lesions. Perhaps the commonest effect of the adult parasite is the obstruction of the circulation of lymph in a part. In some instances, a single worm or a bunch of worms may block the thoracic duct and act as an embolus, or may give rise to a thrombus, or the worm may cause an inflammatory thickening of the walls of the vessel and so lead eventually to obstruction and occlusion. In other instances, the smaller lymphatic vessels, particularly of the glands, may be similarly occluded. As intimated, the occlusion of the lymphatics may prevent microfilariae from reaching the blood stream, and their disappearance may occur immediately after localized lymphatic inflammation. If obstruction by the adult parasites takes place as high up as the thoracic duct, large varicose dilations of the thoraccic and retroperitoneal lymphatics may be produced. Similar obstruction of the large abdominal lymphatics may give rise to chyluria if transudation of chyle through the distended or ruptured lymphatics into the pelvis of the kidney, the ureter, or bladder occurs. Varicose dilations of the lymphatic vessels of the inguinal, iliac, testicular, spermatic regions, and of the skin of the scrotum or labia may also occur. Hydrocele frequently results, and the incidence of hydrocele has been shown in India to be high wherever filarial infection was high; where filarial infection was absent, hydrocele was found to be rare. The lymphatic glands are also frequently affected by the obstruction of the lymph flow, due to more or less acute inflammatory or chronic fibrotic conditions caused from the presence of the adult worms or embryos or their toxins. Living or dead and degenerating worms are very frequently found in the glands, and the dead worms may

be calcified. Inflammation and degenerative changes, as well as disturbances of circulation in the lymphatics, may be brought about by dead or calcified adult parasites.

O'Connor (1932) has concluded from his studies that the adult parasites while alive in the tissues give rise to no serious inflammatory or obstructive phenomena, nevertheless obliterative endolymphangitis may appear. On the death of the parasite, however, conditions are quite otherwise.

Degeneration of the adult parasites may occur in one of three ways: by calcium deposit in the worm, by lymph coagulation, or by a combination of the two. He also thinks that so long as the microfilariae live there is no evidence that they damage the tissues. However, dead worms, undergoing disintegration and absorption, probably liberate toxic substances which may give rise to acute inflammatory changes. The most marked evidence of acute inflammation in his cases was about worms undergoing degeneration. O'Connor believes that the acute inflammatory reaction in filarial lymphan gitis is allergic in character and corresponds to a period when sufficient protein i liberated from recently dead worms to overcome the resistance set up by previous sensitization. Such reactions, when due to minimum amounts of protein, might be subclinical in degree, as seen in localized urticaria, without definite inflammatory attacks, transient rises of temperature, local pain without inflammatory phenomena; while, when large amounts of protein are liberated, the typical inflammatory manifestations of filariasis result. Acton and Rao (1930), in support of this allergic hypothesis, have also reported a series of cases with urticaria and eosinophilia believed to be due to the filarial infection.

The dead, degenerating, and the calcified adult parasites in the tissues of the host may give rise to inflammatory changes even when bacteria are absent. These may be subacute or more chronic, eventually bringing about fibrotic changes. However, the writer has found, particularly in studies in onchocerciasis, that the living parasites may also cause subacute and chronic inflammatory changes. To what extent these are due to the movements of the adult parasites and the almost continuous passage of enormous numbers of microfilariae through the tissues immediately surrounding the adults, and to what extent they are due to toxins, or metabolic products from the parasites, is not clear. The eosinophils are frequently, though not invariably, numerous in the tissues in the vicinity of these parasites. The living adult *Wuchereria bancrofti* in the lymphatics of the host may also give rise to proliferation of the endothelial and connective tissue cells, resulting eventually in the formation of new tissue, and frequently producing chronic obliterative lymphangitis and thickening and enlargement of the part (elephantiasis). In some instances, a lymph thrombosis may form about the parasites. About the adult filariae that are more or less degenerated, infiltration with lymphocytes and plasma cells may be observed to have taken place, with later an invasion with fibroblasts and the formation of fibrous tissue, sometimes encapsulating the parasites. Foreign-body giant cells may also be observed. Such changes may lead to complete blocking and final obliteration of the original lymphatic vessels. O'Connor has also reported that degenerating microfilariae, especially in hydrocele, may cause tissue changes, such as local areas of necrosis and proliferation of connective tissue about them. In one instance, masses of microfilariae were found in a polyp-like growth of granulation tissue at the reflection of the tunica vaginalis. He has also observed the calcified sheaths of microfilariae in the subcutaneous tissues in elephantiasis of the leg.

Location of Adult Parasites.—The adults of both sexes, often inextricably coiled together, live in the lymphatic vessels about the abdominal cavity in particular. They may be found from the thoracic duct downward to the lymphatics of the lower extremities, especially in those of the groin. However, they may be present in the lymphatic vessels in any part of the body. Common sites are the elephantoid tissues of the external genitals and the mammary glands; the lymph glands of the extremities, abdominal retroperitoneal regions, about the kidneys, and the epididymis. In Japanese cases, Miyake found them particularly in the inguinal and femoral glands and in

mammary cysts. In Manson-Bahr's studies, they were situated in superficial abscesses and in the epitrochlear inguinal and femoral glands.

The single worms are so slender that they are very difficult to find in the tissues after death, and when present in abscesses they are often found dead and partially or completely decomposed. Occasionally a small bunch of the parasites is encountered, particularly in the scrotum.

The route by which the microfilariae migrate from the neighborhood of the parent worm and pass from the lymph to the blood vessels, has not been clearly demonstrated. It has been assumed by many writers that they pass from the parent worm by the lymphatic vessels, through the various chains of lymphatic glands to the thoracic duct, and thence to the venous system. However, O'Connor (1931) points out that this has apparently not been demonstrated histologically. He believes, from the careful study of a case, the histologic evidence is to the effect that the microfilariae, after leaving the parent worm, pass through the walls of the lymphatics and enter through the walls of the small contiguous blood vessels.

It had seemed questionable, however, whether sheathed filariae were capable of passing *through* the walls of the small blood vessels. With unsheathed microfilariae, as for example *Onchocerca volvulus*, there is no evidence that they do so. Microfilariae of this parasite are not normally found in the blood vessels. On the other hand, while it may not be possible for sheathed microfilariae to bore their way through the walls of blood vessels and actively penetrate tissue, it seems not unreasonable to assume that in many instances rupture of the small lymphatics and blood vessels may occur, through inflammatory reaction and swelling, and thus an additional opportunity be given for the entrance of the microfilariae into the blood stream. Moreover, experiments performed by Drinker and his associates (1935) show that the unsheathed microfilariae (*Dirofilaria immitis*) may readily get out of unbroken capillaries, traverse a certain distance in the tissue, and enter the lymphatics.

Dhayagude and Amin (1942) in pointing out the absence of records of filarial lesions of the spleen found in 11 spleens at autopsy, lesions which were detectable by the naked eye varying in size from 2 mm. to 25 mm. Usually they were multiple but occasionally only a single nodule was present. Histologically the swellings were granulomatous, and microfilariae, subsequently identified as *W. bancrofti*, were found in each. There was marked local or general eosinophilia and in some sections giant cells were conspicuous. Klotz in *Loa loa* infections found pin-point yellowish nodules in the spleen containing microfilariae, about which there was some inflammatory reaction and fibrosis.

Pathology of Elephantiasis.—There has been considerable discussion as to whether the form of elephantiasis so common in many tropical countries is actually of filarial origin. However, there is a very large amount of evidence which goes to show that while some cases of elephantiasis occurring in tropical countries, just as in the temperate zones, are not of filarial origin, there is a common form of elephantiasis undoubtedly due to filaria. Some of the most striking facts leading to such a conclusion are summarized by Manson-Bahr, as follows:

(1) The geographical distribution of *Wuchereria bancrofti* and that of elephantiasis correspond; where elephantiasis abounds, there the filaria abounds, and vice versa. (2) Filarial lymphatic varix and elephantiasis occur in the same districts, and frequently concur in the same individual. (3) Lymph scrotum, unquestionably a filarial disease, often terminates in elephantiasis of the scrotum. (4) Elephantiasis of the leg sometimes supervenes on the surgical removal of the lymph scrotum. (5) Elephantiasis and lymphatic varix are essentially diseases of the lymphatics. (6) Filarial lymphatic varix and true elephantiasis are both accompanied by the same type of recurring lymphangitis. (7) As lymphatic varix is practically proved to be caused by the filaria, the inference appears to be warranted that with rare exceptions the elephantiasis of warm climates—the disease with which lymphatic varix is so often associated and has so many affinities—is attributable to the same cause.

As has already been intimated, in the majority of cases of elephantiasis, the microfilariae are absent from the peripheral circulation, and it has been pointed out that this is usually true on account of the obstruction and fibrotic changes in the lymphatics which have been brought about by the action of the filariae or through secondary bacterial infection. In many of the cases of elephantiasis, as well as in other pathologic conditions caused by the parasite, the lymphatic system has been blocked and, hence, there is less likelihood of the microfilariae obtaining an unobstructed passage to the

blood. Also the blocking of the lymphatics may cause the death of the adult filariae. Hence filarial elephantiasis may be regarded as a late sequel of filarial disease in which there are frequently no longer microfilariae in the circulating blood, the part becoming progressively larger following repeated attacks of lymphangitis and fever.

Anatomically there is a condition of hyperplasia and hypertrophy of the skin and subcutaneous tissues in a part of the body in which lymphatic and often venous obstruction has occurred. It is the higher degrees of lymphatic hyperplasia, in which there is tumor-like solidity, which are termed elephantiasis.

Histologically the condition varies greatly according to the inflammatory stage. There is primarily an acute inflammation of the corium and subcutaneous tissue; later, hypertrophy and oedema in which there is more diffuse inflammation, dilation, and sometimes thrombosis of the lymphatics, veins and arteries; and finally hyperplasia of the connective tissue cells and cellular infiltration with polymorphonuclear, eosinophilic leucocytes, macrophages, and plasma cells distributed about the lymphatic vessels. In the earlier stages where the tissues are softer and grayish-white, there is usually much mucoid oedematous tissue. The consistency, however, varies, and some areas are composed of richly cellular granulation tissue. In these, the plasma cells are frequently numerous, both in the skin and subcutaneous tissues and numbers of them are multinucleate. Large ovoid mast cells may also be present. The collagen material becomes gradually increased in bulk and arranged in coarse bundles parallel to the skin. Finally there is more marked hyperplasia of the connective tissue, and a general fibrosis results, the soft swelling having given way to the hyperplastic tissue. In advanced cases, the intramuscular tissues may also be infiltrated by the connective tissue growth and the vessels, muscles, fat and nerves gradually destroyed. The skin becomes greatly thickened. It may measure several inches in thickness and be very dense and fibrous. Beneath it the tissues may be very oedematous and blubbery and contain much lymph. The skin is sometimes smooth, but frequently is papillary or verrucous, and sometimes nodular, from the hard hyperplasia of the cutis and subcutis. Sometimes it shows deeper pigmentation than is normal.

While *Wuchereria bancrofti* is apparently the commonest cause of endemic or tropical elephantiasis, bacterial infection may also bring about a similar condition. Also there are congenital and sporadic forms of different etiology. Shattuck (1910) in an excellent article has enumerated and discussed these various forms, and Kaufmann and Reimann (1929) have given further details of the pathology.

Manson-Bahr (1936) recognizes from a clinical standpoint the following forms of elephantiasis in man:

(1) *Congenital or familial*—generally known as Milroy's or Meige's disease, stenosis of main lymphatic trunks.

(2) *Parasitic*—due to *W. bancrofti* or *O. volvulus*.

(3) *Septic*—lymphatic infection by streptococci.

(4) *Toxic*—by absorption of irritating toxins, such as chrysarobin.

(5) *Obstructive*—due to tuberculous glands, carcinomatous growths, syphilis, or yaws, or to surgical removal of main chains of glands.

(6) *Venous*—secondary to venous thrombosis, such as *phlegmasia alba dolens*, or white leg, in parturient women.

The opinion has been rather generally expressed that lymphatic obstruction alone does not give rise to tropical elephantiasis. Actually, our knowledge of the exact cause and manner in which elephantiasis occurs is, in certain particulars, still obscure.

The pathologic changes which occur in the tissues in the immediate vicinity of the parasites consist of an inflammatory reaction, sometimes with necrosis followed by fibrosis. These changes probably result from toxic secretions of the parasite, from mechanical irritation produced

by their activity, or from products of the disintegration of the parasites after their death.

The role which bacteria, particularly streptococci, play in the production of lymphangitis and elephantiasis, has long been emphasized, and it seems clear that elephantiasis often results following repeated bacterial infection of the lymphatic system which has already been damaged by the presence of the filarial worm.

However, there has been much recent controversy about the significance of bacteria, particularly streptococci of the hemolytic variety and staphylococci, in the production of the condition. From the discussion already given in this article of the pathologic changes produced by the living or dead filariae independent of the action of bacteria, it seems clear that the filariae may be the primary exciting factor. In many instances, however, bacteria undoubtedly play an important role. Indeed, the conditions produced by circulatory disturbance in the early stages of the disease constitute a most favorable medium for the multiplication of streptococci and staphylococci.

The observations of Anderson in British Guiana, Acton and Rao in India, and of Suarez in Puerto Rico and Grace and Grace in British Guiana, emphasize the importance of the hemolytic streptococcus in the production of elephantiasis. Grace (1934) concludes that elephantiasis is a manifestation of hypersensitiveness to this organism. On the other hand, McKinley (1931) in Puerto Rico, who made a study of 38 cases of acute filarial lymphangitis, found that blood cultures in all were negative. Cultures made from aspirated material from focal areas of pain and inflammation were negative in 27 cases. In cultures prepared from the skin removed from inflamed areas of 11 cases, one culture was positive for a green-producing streptococcus, another showed a haemolytic *Staphyloccus aureus*, and a third a Gram-positive bacillus. In no case was the *Streptococcus haemolyticus* isolated. In 9 control cases in which the diagnosis was septic lymphangitis *Streptococcus haemolyticus* was isolated in 7 and *Staphylococcus aureus* in 2 cases. He concludes that there may exist in at least 3 types of acute lymphangitis: (1) lymphangitis of bacterial origin: (2) lymphangitis of filarial origin; and (3) filarial lymphangitis with secondary bacterial infection. In his opinion, all the evidence suggests that acute filarial lymphangitis may commonly exist as a disease entity without a complicating secondary bacterial infection. He admits, however, that the mechanism by which the filarial process produced these attacks, without the intervention of other infections, is still unknown.

O'Connor (1932) and Giglioli (1933), from other observations, conclude that the presence of streptococci and staphylococci in filarial disease have significance only as secondary invaders, while Suarez (1933) emphasizes that although the filariae may be the cause of the lymphatic obstruction in many cases, that the patients sooner or later always become victims of bacterial invasion, particularly with the streptococcus, and that the role of infection is the *sine qua non* in the formation of elephantiasis.

Bertwistle and Gregg (1928) believe that elephantiasis may develop in part as the result of excessive protein from lymphatic exudate. The exudate is present as the result of infection, most often streptococcal, increasing in a part primarily presenting venous or lymphatic stasis. They point out that apparently another factor besides lymphatic and venous obstruction is necessary for the development of elephantiasis, as suggested by (1) the presence of solid oedema for long periods without the appearance of elephantiasis; (2) its development in cases of solid oedema after attacks of fever and lymphangitis. It appears necessary, therefore, that not only must there be a transudate of lymph, but that it must be changed in some way, as happens when it becomes an exudate resulting from inflammation. The lymph exudate in cases of elephantiasis, charged with albumin and protein, is a stimulant to cell activity and growth. Hypertrophy and hyperplasia result.

Starling (1925) has pointed out that the only way the tissues can receive their supply of protein is from the small amounts which are filtered through the blood vessels into the lymph. The increased exudation of concentrated lymph which occurs in inflammatory conditions as the result of injury is, therefore, of advantage, since it furnishes an abundant supply of protein food to be used up in the regeneration of the damaged cells.

Bertwistle and Gregg further point out that in elephantiasis the affected part receives an increased supply of protein as the result of recurring attacks of inflamma-

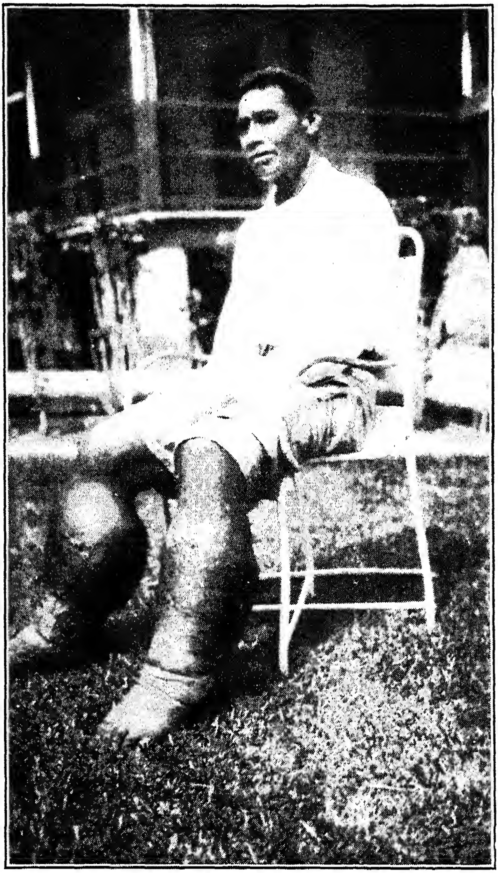

FIG. 299.—Elephantiasis of the legs—a Samoan case.

tion, and it is suggested that this protein, instead of merely helping in the process of repair, serves by its continuous or perverted action to stimulate the connective tissues to excessive growth.

Drinker and Field more recently (1933) made a very careful study of the conditions governing the removal of protein deposited in the subcutaneous tissues of the dog, as well as the cell and protein content of mammalian lymph and the relation of lymph to tissue fluid. They have also studied the permeability of the capillaries of the dog to protein, and show that there is a constant transudation through capillaries of a fluid containing protein with eventual removal of the protein by the lymphatics.

In complete lymphatic obstruction, the lymphatics are constantly engaged in removing blood protein which reaches the tissue and fluid from the capillaries. If the

lymphatic drainage is blocked, and the blood circulation normal, but one result can be expected, namely, the amount of protein in the tissue fluid must rise to an abnormally high concentration. This will be due to the fact that protein will leak steadily from the blood capillaries and, owing to the reabsorption of water by these vessels, there must be an increase in concentration of the protein which they cannot absorb and which cannot get out of the part by the usual lymphatic route. In addition to blood proteins, it is probable that broken down white blood cells must also accumulate, so that the normal cellular environment in the part is converted into one containing a high percentage of blood protein, plus products of cellular disintegration, both of which components would be steadily removed if the lymphatics were functioning normally.

Experimentally they have been able to produce persistent lymph oedema in the leg of a dog through the injection into the large lymphatics of mixtures of oxalated blood plasma plus crystalline silica and calcium chloride, or by using 2 per cent quinine hydrochloride with silica. The first injection results in a swollen leg, but in two to four days it subsides. The operation is then repeated at intervals. In one dog, from the normal leg the lymph contained 0.71 per cent of protein, and from the swollen leg 1.98 per cent of protein, with 7,900 white cells, mostly polymorphonuclear leukocytes, and 6,200 red cells per cubic millimeter, the high cell count being probably a foreign-body reaction to the deposited fibrin.

With reference to the matter of infection in connection with the development of fibrous overgrowth, they point out that under circumstances of infection in a part with obstructed lymphatics, the result can only be intensification of the findings postulated from lymph blockage alone. Under such circumstances the tissue becomes clotted, blood plasma enmeshing cells in various stages of disintegration. There is no drainage for any of this material. It must remain as deposited to undergo slow solution. In their opinion, this abnormal tissue fluid acts as a culture medium, just as it does in tissue culture experiments outside the body. The first group of cells to grow actively are the fibroblasts. This is true in tissue cultures, and it is apparently true in the body when a medium is present rich in blood protein and the products of cell destruction. When high degrees of venous obstruction accompany lymphatic obstruction, the blood capillaries also leak proteins in high concentrations, and again the environment for fibrous overgrowth is provided in more intensive form.

From more recent experiments upon dogs, Drinker, Field and Homans (1934) conclude that experimental elephantiasis may be called forth in a typical form by lymphostasis alone and that it may, without other influence, progress to an advanced state of fibrosis and deformity. In the experimental and human diseases, the same high protein concentration in the tissue fluid occurs. Both lymph and tissue fluid in this condition have from 2.7 to 5 per cent protein, instead of the normal 1 per cent. As this concentration rises toward that of blood serum, fibrosis also increases and aggravates lymphostasis, so that a vicious circle of protein concentration and fibrosis is set up. Once elephantiasis is established in the experimental, as well as in the human, disease, there may set in the same recurrent attacks of fever and local inflammation, usually spoken of as lymphangitis. Haemolytic streptococcus can be cultivated from the tissue fluids in the early hours of each attack in the dog, and at no other time. The same bacteria may call forth a typical attack in another animal, when injected in appropriate quantity into a lymph-obstructed leg and not when injected in even much greater quantity into normal tissue. The resemblance of the elephantiasis produced in one dog to human elephantiasis was striking.

In summarizing this discussion we may say that obstruction of the lymphatic vessels and bacterial infection are the two most important agents to be recognized in the causation of elephantiasis. When such obstruction has been established, acute lymphangitis almost invariably follows. The lymphatics in the condition of lymph oedema receive an increased amount of protein as a result of the inflammation, which serves by its action to stimulate the connective tissue to excessive growth,

resulting in fibrosis of the skin and subcutaneous tissue. In tropical countries, the adult filariae are the commonest primary cause of the lymphatic obstruction. In the great majority of cases, infection with cocci, particularly streptococci, ultimately ensues. Nevertheless, elephantiasis in the tropics, as well as in temperate climates, may result entirely independently of filarial infection.

CLINICAL MANIFESTATIONS

Filarial Diseases.—The important pathologic conditions associated with infection with *Wuchereria bancrofti* are related to the lymphatic system.

They are (1) inflammatory, giving rise to lymphangitis and elephantoid fever, lymphadenitis, orchitis, and inflammatory varicose groin glands, and abscess; secondary infections with streptococci and staphylococci, and sometimes giving rise to fatal peritonitis; (2) dilation of the lymphatics without rupture, giving rise to varix lymphaticus, cutaneous and deep, and producing conditions such as lymph scrotum; or adenovarix; (3) dilation with rupture, giving rise to lymphorrhoea and lymphuria or chylocele; chylous acites; chylous diarrhoea and chyluria; (4) hypertrophy, hyperplasia and fibrosis, giving rise to elephantiasis of the leg, scrotum, arm, mammae, and other parts.

Lymphangitis, Elephantoid Fever and Adenitis.—The febrile accessions that accompany the recurring attacks of lymphangitis in elephantiasis, lymph scrotum and other filarial manifestations are very important because they may lead to errors in diagnosis. Thus in Barbadoes, where until recently there was little or no malaria, a condition in which there occurs a high fever of sudden onset with rigors and sometimes, though not always, associated with erysipelatous redness of leg or scrotum and by lymphangitis and painful lymphatic glands, has given a suggestion of a malarial paroxysm.

Lymphangitis.—The condition of lymphangitis may be dependent upon the irritation caused by the presence of the filaria which may be either alive or dead in a lymphatic vessel. As a result, the lining endothelium of the lymphatic may become proliferated, necrotic and desquamated, and the contents of the vessel coagulated. Infection with either streptococci or staphylococci is common, in which case the process may go on to suppuration with formation of an abscess in which the dead or calcified filariae may be found. In some instances, resolution occurs. In chronic lymphangitis there is great proliferation of the intima, more or less complete blocking of the lumen, and general fibrosis of the walls, so that the vessel becomes thickened. Filariae may be found in the vessels, sometimes embedded in the fibrous tissue or in a caseous mass; in other instances, in cyst-like dilations of the lymphatics, as described by Maitland, Daniels, Manson-Bahr and others.

The attack of lymphangitis may be preceded by a fit of shivering and is always accompanied by fever, often lasting several days and varying from 101° to 104°F. Also there may be severe headache, vomiting, and some delirium, rarely suppression of urine and albuminuria. The affected

part is oedematous and often painful to the touch. If the extremities are involved, the swollen lymphatic vessel may be palpable as a hard, cord-like substance, which is often visible; the skin is diffusely reddened or erysipelatous in character, or red congested streaks may be seen over the inflamed lymphatic vessels. After several days the swelling of the limb usually begins to subside and the attack may end with profuse diaphoresis. A lymphous discharge may occur from the surface of the skin. In other instances, infection with streptococci or staphylococci may lead to abscess and even to gangrene, especially if the scrotum is involved. In some instances, the part appears to return to its normal condition; in others the skin may remain more or less infiltrated. At various intervals of time, weeks, months or years apart, similar attacks may recur, eventually leading to hypertrophy and perhaps to elephantiasis. The microfilariae may be present or absent from the blood, or they may disappear during the attack, not to reappear. The inflammatory process may not be limited to the superficial vessels, but may be particularly in the deep lymphatics. Those of the spermatic cord, testes, and retroperitoneal tissues are frequently involved.

Elephantoid fever may occur at varying intervals of weeks, months, or years, in association with most forms of filariasis. In Barbados, where sometimes malaria has been suggested, it has been commonly called "ague"; in Fiji it is termed "liliwa" (Castellani) and "wanganga" (Manson-Bahr). In India this form of recurrent fever has been attributed by Banerjee to mysterious lunar influences. The onset of the fever is usually sudden and the temperature may reach 102° to 104°F. It is often accompanied by rigor and sweating. The temperature may touch normal within 24 hours or it may last several days. In some cases, especially those associated with elephantiasis, the fever may last a month or so (Stephens and Yorke). Microfilariae may or may not be present in the blood. In many cases, the fever is associated with lymphangitis, but in other cases the paroxysms may occur independently of lymphangitis. In such cases, the reason for the rise of the temperature is not always clear. Manson-Bahr suggests that in this form there may be an inflammation of the deep-seated lumbar lymphatics or glands which are not visible.

Lymphadenitis of the associated glands usually accompanies the attack of lymphangitis, or it may precede it. The enlarged glands are usually painful during the attack.

However, in other instances the groin glands may gradually assume a varicose condition and considerable size without any noticeable symptoms. Both groins or only one may be affected, or the femoral glands of both sides may be involved. Sometimes the condition is associated with lymph scrotum. The soft swellings may be small or reach anywhere from about 5 to 8 cm. in diameter. An attack of lymphangitis frequently involves them in the inflammatory process. In such cases, tenderness and painful symptoms may appear and streptococci may be present in such glands. Rogers and Megaw and Manson-Bahr call attention to the fact that these swellings of the inguinal glands with varicose lymphatics may sometimes be mistaken for hernia, and Manson-Bahr emphasizes that chronic swellings about the groins and testes and scrotum

in patients from the tropics should always be regarded as possibly filarial in nature After hernia has been excluded in these cases, removal of a few drops of lymph with a hypodermic needle may reveal, on microscopic examination, the microfilariae or ova, or the microfilariae may be found in the circulating blood. Frequent attacks of lymphangitis in these glands leads to fibrotic changes and great enlargement. In some of the Pacific Islands, notably in Fiji, great enlargement of the lymphatic glands with fibrotic changes was found by Manson-Bahr to be by far the most frequent symptom of filarial disease. The epitrochlear gland in Fiji was found to be affected in 22 per cent of the total population. The groin glands were also very much enlarged, sometimes 5 to 7 cm. in diameter, and might form permanent tumors. The deep-seated glands, iliac, lumbar, mesenteric and mediastinal were also sometimes enlarged. On dissection, live filariae or calcified parasites were in some instances demonstrated in the glandular substance.

Funiculitis, lymphangitis of the spermatic cord, is common, and is frequently associated with lymphangiectasis, in which cases the cord is acutely tender and the scrotum inflamed. Hydrocele may also exist and there may be inguinal adenitis. In severe cases, secondary infection sometimes occurs, often accompanied by frequent rigors. Septicaemia may result, and then death not infrequently occurs. In some instances, at postmortem examination purulent lymphangiectasis and purulent infiltration about the vas deferens have been observed. Sorour (1929) has recognized as common in Egypt a chronic eosinophilic funiculitis, characterized by fibrosis, heavy eosinophil infiltration, and thickened blood vessels which are often thrombosed. Filariae were found in the tissues in each case.

Filarial orchitis and **hydrocele** are also common conditions. The orchitis usually begins with pain in the testicle, accompanied by fever and sometimes by rigors. The testicle enlarges rapidly and may sometimes reach the size of some 10 cm. in diameter. It is tender and painful. An effusion usually forms in the tunica vaginalis. Persistence of the lymph, which may become coagulated, may give rise to filarial hydrocele, lymphocele, or chylocele may result. The swelling may subside completely in a few days or may leave a permanent thickening. Recurrences of the attack are common.

Involvement of the retroperitoneal lymphatics may also give rise to a serious condition. Stephens and Yorke classified under this term the conditions described by French writers as "filarial colic," and probably the "fever and ague of the abdomen" of other writers. It is characterized by acute abdominal pain, vomiting, hiccough, rigidity of muscles, meteorism, at times by retention of urine, and usually by fever. Wise also described a similar condition in British Guiana under the term "filarial septicemia." Anderson, who has especially observed this condition, points out that the symptoms of peritonitis are rapidly developed, and that a streptococcus is invariably present in these cases. In Wise's cases the condition was found post mortem to be an acute suppurative inflammation of retroperitoneal lymphangiovarices; the dilated lymphatics were filled with pus. Adult filariae were found in the pus in 3 of the 30 cases examined. The abdominal lesion was a secondary one, and in every case, with one exception, was connected with a similar lesion outside the abdominal cavity, as, for example, in the glands of the inguinal, cervical or axillary regions, or with suppurative lesions of the scrotum and cord, or abscesses in the leg or arm. Streptococci were frequently found in the affected lymphatics.

Hydrocele.—The condition often suggests in the beginning a simple attack of epididymitis. A common result of inflammation or of blocking and dilation of the lymphatics in the region of the testicle is effusion into the tunica vaginalis. Low points out that a favorite site of the adult

filaria is the epididymis, and if it sets up inflammatory changes here a hydrocele is often produced. Hydrocele or chylocele, according to whether the exudate is straw-colored and lymphous or milky and chylous, is often associated with orchitis, or may begin with symptoms resembling epididymitis. It is a very common complication of filarial infection, and in the Philippine Islands it is perhaps the most common pathologic manifestation of filariasis. Buxton (1928), is Samoa, and Rao (1932), in India, have shown that there is a relatively high coefficient of correlation between the presence of microfilariae in the blood and the presence of hydrocele.

In 21 cases observed in Samoa, the microfilariae could be demonstrated either in the blood or the hydrocele fluid of 12. Rao found that in the district of Cuttack, which showed the highest filarial infection (microfilaria rate 25 per cent), also showed a high incidence of hydrocele (15 per cent). Grace and Grace, in British Guiana, found the microfilariae rate of infection (both sexes) 23.1 per cent, and the hydrocele rate (in males) 12.3 per cent. Microfilariae are frequently absent in the hydrocele fluid. Rao, in 143 cases, found microfilaria present in 14, but O'Connor, in Puerto Rico, failed to find them present in 20 cases.

The condition is in many instances independent of any secondary bacterial infection. In other cases, however, when the condition is associated with orchitis and a sudden febrile onset, secondary infection with cocci is usually present. Buxton found in 70 per cent of the patients carefully examined at operation that the condition was bilateral, suggesting trauma or secondary infection as an important factor in etiology in such cases, rather than blocking on both sides with filariae. O'Connor (1929) and Manson-Bahr report cases showing that hydrocele may often result from repeated attacks of filarial lymphangitis in which cases the sac is generally thickened and often contains calcified filariae.

Lymphorrhoea.—The lymph or chyle may escape from the lymphatics in other parts of the body; for example, from the superficial lymphatics, appearing on the surface of the skin, after attacks of lymphangitis. Also, infiltration and chylous effusion of the tunica vaginalis may occur and give rise to chylocele, which Manson-Bahr has found not to be uncommon, and which is sometimes associated with lymph scrotum or with adenovarix.

Chyluria.—One of the most striking pathologic conditions associated with filariasis is that of chyluria. This results, first, from obstruction to and dilation of the thoracic duct or of some of the abdominal lymphatic vessels communicating with those which carry the chyle from the intestine. Finally, the rupture of some of these through the mucous membrane of the urinary tract takes place, with the result that chyle appears in the urine, frequently rendering it milky in appearance. Owing to the general congestion and dilation in the region, rupture at the same time of some of the smaller blood vessels may also occur, when blood, in addition, appears in the urine and haematochyluria results.

The urine in this condition may assume various shades of pink or rose. In many instances the ruptured lymphatic contains no chyle, and then only lymph appears in the urine and the term lymphuria, as originally suggested by Low, is more appropriate, or, if blood is present, haematolymphuria. The chylous urine obviously contains a larger amount of fat derived from the lacteals of the intestine. It usually coagulates rapidly and after standing there separates an upper fatty layer and a pink or rose-colored sediment with a semi-transparent gelatinous layer of coagulated lymph between. The color of the urine varies according to the amount of chyle or blood present. Usually

the morning urine is less milky and contains less blood. Sometimes it has the appearance of *café-au-lait*, or may be reddish. Albumin is always present. In chyluria the fat, according to the investigations of Young, frequently amounts to between 1.8 to 2.6 per cent. The sediment of the urine usually reveals lymphocytes and a variable number of red blood cells, and frequently microfilariae. However, the latter are not always present, but their absence does not exclude filariasis. Minami and Ehara report a case in which microfilariae were present neither in the night blood nor in the chylous urine; nevertheless, on removal of the kidney a female filaria, apparently alive, was found in a lymphatic gland about the hilus of the kidney. Microfilariae were present in the fluid about it. The escape of chyle may occur into the pelvis of the kidney, the ureter, or bladder, and the chylous fluid may undergo spontaneous coagulation and give rise to obstruction of the ureter or urethra, and retention of urine. In 2 cases reported by Minami the coagulation of the chylous urine occurred in the pelvis of the left kidney, and in each case the pain and discomfort were said to render removal of the kidney necessary. The kidney showed hyalin degeneration of the convoluted tubules with exuded plasma in the lumen and in many of the glomerular capsules. Minami and Ehara state that changes in the kidney were evident in 76.5 per cent of the cases of chyluria they collected from the literature.

The attack of chyluria is usually abrupt. Sometimes it is preceded by pain in the back or aching sensations in the lower abdomen, thighs, and peritoneum, perhaps due to the great distention of the lymphatics involved. At times the attack is accompanied by fever; in other cases, retention of urine due to coagula or the passage of milky or reddish urine may first attract attention to the condition. The attack usually lasts only for a few days, particularly if the patient remains in bed, but more rarely it may persist for a considerable period. Recurring attacks are usual, with intermissions lasting days, months, or years.

In mild cases, the health does not suffer, but in serious ones, with the loss of large amounts of albumin, debility, depression, and anaemia may result. Retention may give rise to more serious disturbances and injury to the kidney. Although chyluria in India, China, Japan and North Africa is frequently observed in association with filariasis, it is a curious fact that it is extremely rare in the Pacific Islands. Buxton recorded only 2 cases from Samoa during his investigations there through some two years. Anderson (1924) found that among 709 patients who visited his clinic in British Guiana, orchitis was found in 1.9 per cent and chyluria in 1.5 per cent, while Grace and Grace (1931) found in their examinations in British Guiana only 0.4 per cent affected with chyluria.

Chylous Ascites.—Very rarely the chyle may escape into the peritoneal cavity, giving rise to chylous ascites, or into the intestine, giving rise to chylous diarrhoea. Wise has reported a case of chylous ascites diagnosed by abdominal puncture. At necropsy a large cyst was found occupying the whole abdominal cavity. It had apparently developed between two layers of the mesentery. Breinl and Priestly have also reported a case of chylous ascites which died with the symptoms of acute peritonitis. Froes (1933) has reported the presence of numerous microfilariae in a case of ascites. The fluid obtained by tapping repeatedly contained the microfilariae, but was nonchylous and nonhaemorrhagic. The microfilariae were also present in the blood. The microfilariae were neither periodic in the blood nor in the effusion.

Lymph Scrotum.—In the condition known as lymph scrotum, the onset is often with fever, followed by more or less enlargement of the part and varicose and tortuous lymphatics. The varices may be seen and felt. In some instances, the scrotum appears covered with numerous small vesicles; these may vary from several millimeters to even a centimeter in diameter. When one of these vesicles or a tortuous lymphatic is pricked or ruptures, an exudate of milky or blood-tinged lymph or chyle exudes, which rapidly coagulates. Microfilariae are usually present in this exudate. In cases with con-

siderable enlargement of the scrotum, 500 cc. or more of fluid may exude in 24 hours, and this exudation may continue for several days. Stephens and Yorke report that in some cases periodic discharges may occur for two to three years, threatening the life of the patient from exhaustion and necessitating removal of the scrotum. In many cases, lymph scrotum is associated with enlarged or varicose glands of the groin and with chyluria. A gradual transformation from lymph scrotum to elephantiasis of the scrotum may occur, with erysipelatous manifestations. Lymph scrotum, while not uncommon in parts of Asia, is practically unknown in the southern Pacific Islands as a complication of filariasis.

Acton and Rao (1930), who report 9 cases of lymph scrotum, point out that in every one there had been an antecedent operation for hydrocele. They take the view that hydrocele or chylocele is really an overflow reservoir for lymph dammed back by fibrosed lymph nodes and that when the sac is removed its function is taken up by a dilation of the lymph vessels which may result in lymph scrotum. Microfilariae were present in the lymph from the scrotum in 7 cases, but in only one of these in the blood.

Varicose Groin Glands (Adenovarix).—Lymphadenitis associated with lymphangitis has already been discussed, page 1316.

FIG. 300.—Varicose lymph glands. (After Taniguchi-Kumamoto.)

The term "varicose glands" (referring especially to the glands of the groin or of the axilla) has been used by Manson and others for many years to imply the soft, more or less lobulated swellings in which dilation of the lymph vessels have occurred. Stephens and Yorke have used the term *adenovarix* for this condition, which they state is probably usually associated with lymphangiovarix. The skin over the enlarged glands can generally be freely moved. These swellings, which usually develop slowly, may involve the inguinal or femoral groups of glands of one or both sides. The commonest site is the fold of the groin of the upper internal aspect of the thigh, but the lesion may also occur in the axilla. In the groin, it is commonly associated with lymph scrotum and sometimes with chylous dropsy of the tunica vaginalis or with chyluria. The varix may be single, as large as an orange, or forming a huge mass reaching to the knee, or there may be several varices from one to several centimeters in diameter. On palpation, the sensation of coiled rubber tubes which collapse on firm pressure may be obtained. Usually painless and insidious in onset, the condition may become acutely inflamed and accompanied by fever. Puncture yields a fluid which may or may not contain microfilariae. The condition is commoner in the male sex.

Filarial Abscess.—As a rule, injury to the adult filarial worms which results in their death is not followed by abscess formation, but such termination may occur. As

regards location, Wise and Minot found filarial abscesses 31 times in the pelvis of the kidney, 18 in the epididymis, 12 in the retroperitoneal tissues, 25 in the inguinal glands, 4 in the ilio-psoas muscles, and 8 in the lymphatic vessels.

Stephens and York emphasize that the disease may or may not be associated with the presence of filaria in the abscess. Kennard failed to find filaria in 2 abscesses examined by him and Maxwell found adult filaria in only 1 of 23 abscesses; while Manson-Bahr found adult filaria in 1 of 8 superficial abscesses. Wise found filaria in 22 of 28 superficial abscesses, in 3 of 30 retroperitoneal abscesses, and in 10 of 15 abscesses, involved in the epididymis. The pus usually contains pyogenic organisms, but may be sterile. Manson-Bahr, who examined 8 cases bacteriologically, found staphylococci in 6, streptococci in 1, and both organisms in 1; while Wise, in 28 cases, found staphylococci in 4, streptococci in 21, while 3 were sterile. Anderson, in a study of filariasis in British Guinana, met with nearly 50 abscesses, but found parts of adult filaria in only 2. In the examination of 48 abscesses, streptococci were found in 41, staphylococci alone in 5, diplococci in 1, and one abscess appeared sterile.

Secondary Infections.—The investigations of Anderson emphasize the importance of bacterial infection in fatal cases of filariasis. He had the opportunity of performing postmortem examinations on 28 cases which showed evidences of elephantiasis and filariasis. The cause of death in 14 out of the 28 cases was acute septicaemia. The cases of acute septicaemia were generally diagnosed as abdominal filariasis.

In each of these cases, the acute septicaemia took its origin from some inflammatory focus in the lymphatic system and ended with great septic engorgement of the retroperitoneal lymph channels. The other common factor in all of these cases was the presence of filarial parasites, and he remarks that it remains a difficult problem to assess the pathologic potentialities of this factor. He pointed out that some investigators have put forward the suggestion that the chain of symptoms may arise from blockage of some part of the lymphatic system, particularly the thoracic duct, by one or more adult filariae in a dead or dying condition, but in none of the cases examined by him or by his colleagues was there any evidence of complete occlusion of the lymph channels by coils of worms. Others have suggested that the parasite exercises a purely mechanical function in carrying the pyogenic organisms from the peripheral into the deeper lymphatics. The experience in British Guiana suggests rather that the adult filariae, living and moving about in the lymphatic system, prepare the ground for bacterial invasion. They may irritate or damage the interior of the lymphatics and the fine internal structure of the glands and a moderate bacterial invasion is sufficient to blaze the trail. Anderson points out that in a tropical country like British Guiana, where streptococci are so prevalent and abrasions of the skin such a common occurrence, where mosquitoes are so active and the general filarial rate so high, the serious incidence of acute septicaemia might thus appear to have a reasonable explanation.

Grace and Grace found at St. Kitts, British West Indies, that when an abscess was found in association with lymphangitis, the *β haemolytic streptococcus* was recovered from the abscess in 26 of 27 cases, and that in 5 of these 26 cases the same microorganism was recovered from the blood, and it was present also in one case of abdominal filariasis. They did not believe, however, that their evidence showed that *Filaria bancrofti* was capable of producing the lymphangitis.

Grace (1943) after further study believes that the existence of lymph stasis renders the tissues more susceptible to infection by the beta-hemolytic streptococcus and that attacks of lymphangitis may then be occasioned by organismal or toxic stimuli of intensity too low to be appreciated by tissues previously uninvolved.

Elephantiasis.—This is one of the commonest lesions. Its prevalence varies considerably in tropical countries, but is obviously related to the degree of filarial infection. In certain districts in Cochin China, about 5 per cent of the population show the condition; in areas in Samoa about 48 per cent; while in the island of Huahine, Society Islands, 70 per cent of the adult male population have been reported affected, by Manson-Bahr.

In the Ellice Islands, with a population of 3,300, O'Connor found 120 cases. The condition is also very common in the Belgian Congo and in many other tropical and subtropical countries. It is rare or absent, however, in large areas of South Africa; for example, Rhodesia (Blackie, 1932). The British Filariasis Commission in British Guiana reported that at one time the proportion of people in Georgetown suffering from elephantiasis was probably higher than in any other city in the world. Yet, in their studies made in 1921, in a limited area they found the rate at most was not over 5 per cent of the population. In 1931, Grace found the rate of elephantiasis in British Guiana to be 11.4 per cent. The condition was also formerly very prevalent in Barbados, and is still popularly known in British Guiana as "Barbados foot." In some regions where infection of the blood with microfilariae is common, elephantiasis is rare or absent. Thus, Crichton (1929) in the British Solomon Islands, whose survey showed 15 per cent of the inhabitants to harbor larval filariae in the blood, found elephantiasis very rare, while Croll in Brisbane, Australia, reports that elephantiasis was never observed in the Australian troops examined, in spite of the fact that 11.5 per cent of the adults had microfilariae in their blood. In this region, the climate was very dry. However, Cilento (1932) reports typical cases of elephantiasis in Queensland.

Buxton feels convinced that in Polynesia and Fiji elephantiasis is commoner in Europeans than in any other part of the tropics and suggests that this may be due to the fact that the non-periodic filaria of Oceania is a day-biting mosquito; that during the day the European is in contact with the native race and more exposed to the bites of these mosquitoes.

The condition is one of adult life and is rare under 20 years of age. After this period, the percentage rises steadily. Grace found that more cases begin in the third decade than in any other.

The statistics of Manson-Bahr show that in 95 per cent of the cases the lower extremities (either one or both, alone or in combination with the scrotum or arms) are the seat of the disease. The foot and ankle only, or the foot and leg, or the foot, leg, and thigh, may each or all be involved. The condition is usually, but not always, confined to below the knee. Rarely the thigh is involved. The swelling may attain enormous dimensions. In extreme cases, the limb may attain a circumference of several feet.

Next to the leg, the scrotum is most frequently involved, and the scrotal tumors may attain an enormous size; 10 to 20 pounds are common weights, and 40 to 50 pounds is by no means an unusual weight. The largest recorded one is 224 pounds.

In elephantiasis of the scrotum, the penis is usually not hypertrophied and is generally incorporated or concealed in the scrotal mass. The testes are often dragged down toward the bottom of the tumor and attached to the under part of the scrotum by the gubernaculum testis, the spermatic cord being thus greatly lengthened. As a rule, there is double hydrocele and thickening of the tunica vaginalis.

The arms, in most countries, are more rarely attacked. However, in Fiji for some unexplained reason, elephantiasis of the arm is comparatively common. Tribondeau found the condition 14 times in 69 cases of elephantiasis observed in the Society Islands. In 12 of the cases, it was secondary to elephantiasis elsewhere in the body, and only 2 cases primary. The condition begins as a lymphangitis accompanied by fever and adenitis of the epitrochlear glands. Repeated attacks of lymphangitis finally give rise to large tumors, or may convert the limb into a shapeless mass.

Rarely the mammae, vulva, penis and circumscribed portions of the integuments of the limbs, trunks, neck or scalp are affected. Cases of elephantiasis of the mammae have been recorded in which the organ descended to the pubis. One such tumor weighed twenty-one pounds after removal. Tumors of the labia or of the clitoris may also attain great size, 8 to 10 pounds in weight. Elephantiasis of the penis is rare. It may occur in the absence of elephantiasis of the scrotum. In some instances, the organ assumes monstrous proportions, as reported by Hazell Wright. Sometimes it becomes as thick as the leg and reaches to the knee. Elephantiasis of the scalp has been reported by MacDonald, and of the thigh by Corney. One such tumor of the thigh weighed 21 pounds after removal. In one case of elephantiasis of the tongue, reported by Kolb in British East Africa, the tongue projected 8 inches from the mouth and the lower jaw was dislocated.

FIG. 301.—Elephantiasis of the scrotum. (Harvard African Expedition—1930.)

Elephantiasis usually begins as a lymphangitis, with fever and secondary dermatitis and cellulitis. Repeated lymphangitic attacks with secondary infections with the pyogenic cocci give rise ultimately to the deformities. In other instances, the onset is insidious, with no history of lymphangitis and no evidence of secondary infection, the condition arising as a gradual, painless swelling. The lymphatic glands draining the affected area are generally enlarged. In elephantiasis of the extremities, the appearance usually varies with the age of the condition. The pathology of the condition has been described on page 1310.

Anderson has distinguished five clinical types: in the first there is usually slight, uniform enlargement, seen more commonly in younger people, in which the limb is oedematous, and there is some thickening of the skin. Beyond the loss of shapeliness and the slight increase in weight, it causes no disability of discomfort. If at this stage the patient is careful about personal hygiene, protects the limb from injury by some form of covering, and practices gentle massage, the progress of the elephantoid condition

may be arrested or it may even disappear. If, on the other hand, the patient is careless of scratches and irritations of the skin, chills may occur and attacks of lymphangitis will interfere seriously with the return flow of the lymph, and hypertrophy of the limb continues.

This gives rise to the second type, which is characterized by marked enlargement of irregular shape and great increase in weight. The skin is thickened to a considerable degree. Subcutaneously there is a great increase of fatty and fibrous tissue. The lymphatics become greatly increased in size and number and the muscles become hypertrophied.

In the third type, the hypertrophied tissues billow out into rounded masses, with deep sulci at the flexures, such as the back of the knee, the front of the ankle, and at the toe joints. The skin is much thickened and coarse, and there is a tendency for a slight abrasion to proceed to deep indolent ulceration. Abscesses are a frequent occurrence in this variety, and the coarse thickened skin often shows the scars of surgical incisions.

A fourth type is the variety known as *Elephantiasis verrucosa*, on account of the very coarse, warty appearance of the skin. The warts and small bosses appear in greatest profusion around the lower part of the calf and on the dorsum of the foot. A number of writers have called attention to this form of *Elephantiasis verrucosa*. Breinl (1910), Buxton (1928), and the writer (1924–25, 1930) have emphasized its association with filariasis and have pointed out that it is not a distinct morbid entity due primarily to infection with a species of fungi, though secondary infection, especially with bacteria is usual.

A fifth type of elephantiasis, seen in cases of longest duration, has the most characteristic elephantoid appearance. The skin is enormously thickened and leathery and is thrown up into rugae. The subcutaneous tissues became greatly hypertrophied, especially around the ankle, and the obliteration of all curvatures gives the suggestion of an elephantine foot. The weight of the limb is frequently sufficient to cripple the patient, and in advanced cases his movements are confined to dragging himself about over very limited areas.

Prognosis.—Apart from the disability produced from the different forms of elephantiasis, the prognosis is good. The condition is a chronic one and patients frequently live for many years, except when secondary bacterial infections, particularly with streptococci, produce septicaemia, when death may occur within a few days.

Rarer Complications.—Manson-Bahr (1928) calls attention to filarial synovitis. He says that its occurrence with filarial invasion is too common to be accidental. Fibrotic ankylosis often results. In cases where the hip joint is affected, removal of the inflamed iliac glands draining the area has in some instances appeared to relieve the condition. In severe cases, the synovitis may even proceed to pus formation, and a fatal result ensues.

DIAGNOSIS OF FILARIASIS

Fresh cover slip films of the peripheral blood, finger or ear, should first be examined with the low-power objective (two-thirds or AA). The actively moving larvae, when present in fair numbers, are usually quick to detect. The specimen should be collected at intervals from 9 o'clock until midnight. If parasites are not found, other specimens should be prepared during the day for the detection of other species of microfilariae.

In many cases, the larvae are very sparse and when not found in fresh preparations, thick films should be made with several drops of blood run together; the specimen allowed to dry spontaneously or with slight heat. The film should then be immersed in water to dissolve the haemoglobin, allowed to dry, fixed in alcohol and stained either with Giemsa's solution or with haemalum. Larvae in the non-motile state may be concentrated by laking blood in 5 volumes of 2 per cent acetic acid and examining the sediment after centrifugalization.

Microfilariae may also be found in the lymph obtained by puncture of a hydrocele or chylocele from a lymph scrotum, or from enlarged lymphatic glands, in the urine in cases of chyluria, and occasionally in blood-stained sputum. The failure to find the microfilariae does not exclude the diagnosis of filarial infection or of pathologic conditions of filarial origin. The passage of the larval forms into the blood stream may be prevented by various pathologic lesions in the vicinity of the adult worm, or the adults may have died after producing the lesions.

Diagnosis of the affection may also sometimes be made by finding the adult filariae, either alive or dead and calcified, in lymphatic glands, in the contents of filarial abscesses, or in other pathologic material removed by operation, as, for example, in elephantiasis. When death and calcification of the adult worms has occurred, roentgenograms are often of considerable diagnostic aid. In the absence of intestinal helminths, the presence of an eosinophilia may be of aid in the diagnosis, particularly when fever is present and a chill has occurred, and the question of malarial fever has thus been suggested. A leucocytosis, such as often occurs in lymphangitis and other inflammatory processes which accompany filariasis and when secondary bacterial infection is present, may also aid in excluding malaria.

Complement Fixation and Cutaneous Test.—Taliaferro and Hoffman, Chandler, and Fairley have suggested these reactions for diagnosis. Fairley showed that a positive reaction could be obtained in most cases of infection with this and other related filariae (a group reaction) by using an antigen made from *Dirofilaria immitis*, the heart worm of the dog.

The worms are thoroughly desiccated and ground, and 0.5 Gm. of the powder is extracted with 50 cc. of 98 per cent alcohol for 24 hours at 37°C., shaking occasionally. This is concentrated by putting it in a water bath at 40°C. and bubbling air through it until it becomes turbid. The turbidity is removed by adding alcohol to a volume of 25 cc. It is preserved on ice in the dark. The usual technique of the Wassermann reaction is followed.

A *cutaneous test* has also been devised, using a 1 per cent saline extract of this powder (2 hours at 37°C.) which has been cleared and sterilized by successive filtration through paper, a Buchner funnel and a Seitz filter.

Fairley injected 0.25 cc. of an 0.1 per cent extract. He points out that only the production of wheals attaining a diameter of 2.4 cm. should be regarded as a definitely positive reaction. In non-filarial cases it was uncommon for the wheal to increase above 2.0 cm. However, natives coming from endemic areas often gave positive skin tests in the absence of collateral evidence of filarial infestation. He presumed that in some instances sensitization followed by natural cure had occurred. While comparatively few cases of active *W. bancrofti* infection had been tested by Fairley with positive results, he believes that by the time elephantiasis due to this worm has developed, the blood test has become negative.

On the other hand, Fulleborn and Sonnenschein (1932) have found that in individuals free of filarial infection, the skin test, with *D. immitis* antigen as well as with Onchocerca antigen, was mostly positive.

Rao (1932, 1934), in employing the skin test in India, used as antigen microfilariae of *W. bancrofti*, hydrocele fluid, with and without microfilariae, and adult guinea worm. "Out of 78 cases tested, including those definitely known to be infected with *W. bancrofti* and control cases, positive reactions were observed in *all* with every one of the antigens used."

Lloyd and Chandra (1933), using as antigen extracts variously prepared of *Dirofilaria immitis*, examined by the complement-fixation reaction a series of 89 cases of various clinical types of infection with *W. bancrofti*. Twenty-three positive reactions were obtained in the series. A series of 15 cases of infection by other helminths was also similarly examined, yielding 3 positive reactions, all of which were in guinea worm disease.

Culbertson and Rose (1944) have prepared an antigen from *Litomosoides carinii* from the pleural cavity of infected cotton rats and have performed both skin tests and complement fixation tests with the antigen diluted to 1:200 in carbolized physiological salt solution. They have used this test in *W. bancrofti* infection as well as infection with *Loa loa* and *Onchocerca volvulus*. However, the reaction is not specific and it seems obvious that further experimental work must be performed before the test can be regarded as of practical value in the diagnosis of *W. bancrofti* infection.

Incidence and Diagnosis in the South Pacific

The instance of filariasis has been increasing rapidly in the Eastern Islands of the South Pacific theater. Clinical symptoms were usually first noted about 9 months after exposure to infection and after 12 months the number of infections increased rapidly. In some localities the increase has assumed epidemic proportions, a total of 319 cases being reported from one theater. Many have been in troops stationed in the Society Islands but a significant number have also been reported in British Samoa, the Cook Islands, Tonga and Tongarava.

Dickson, Huntington and Eichold (1943) have studied 251 cases of acute lymphangitis in our troops in the Samoan region. The following table shows the anatomical distribution of the lesions in these cases. It emphasizes the fact that there were few instances in which the leg alone was involved and they point out that in this region the scrotum was most commonly affected.

Patients with unilateral scrotal lesions only	95
Patients with unilateral arm lesions only	45
Patients with unilateral leg lesions only	4
Patients with bilateral scrotal lesions only	33
Patients with bilateral arm lesions only	11
Patients with bilateral leg lesions only	3
Patients with multiple involvement:	
Scrotum and Arm	49
Scrotum and Leg	6
Scrotum, Arm and Leg	2
Arm and Leg	3

Buxton in a survey made in earlier years made similar observations. Dickson et al, observed that the lesion usually started with a lymphadeni-

tis, then continued as a retrograde or centrifugal lymphangitis. There was a highly characteristic type of scrotal involvement with funiculitis and there was a tendency to multiple involvement and recurrence. Severe constitutional symptoms were absent. The condition of acute lymphadenitis and lymphangitis has been designated by the natives for many years as *mumu*, as was surmised by Buxton to be of filarial origin.

Sapero (personal communication, 1944) recommends the following criteria of diagnosis of filariasis in military personnel in the South Seas.

1. *Diagnosis of Filariasis* (*Wucheria Bancrofti*).—The signs and symptoms of filariasis, which have occurred in military personnel, are often so typical that the diagnosis may be made easily and with certainty. Unfortunately these characteristic signs are frequently not present when the patient first presents himself for examination, and in such instances the difficulties in establishing a diagnosis become great. This, together with the additional fact that many physicians are not too familiar with the disease, makes it desirable to enumerate the various points which should be the basis for diagnosis.

2. *Criteria of Diagnosis.*

A. A characteristic history reveals:

1. *Exposure is an area of known transmission.* Filariasis is endemic in many areas throughout the world in which military operations are in progress. The disease, however, has occurred in troops in significant numbers only in a relatively restricted area, namely, in American and British Samoa, and in Wallis Island. A few cases have been reported from Bora Bora, the Tonga Islands, and Funafuti. A diagnosis of filariasis in an individual not exposed in any of the above locations should be regarded with caution unless the parasite is found. An occasional, relatively rare, case may be encountered whose infection was contracted in the New Hebrides or Solomons.

2. *A prolonged incubation period* characterized by an elapse of many months between the first exposure to filariasis in a known transmission area, and the appearance of the first signs and symptoms. The greater number of cases occur from the eighth to the twelfth month. Shorter (within two months), and longer incubation periods, however, have been reported.

3. *A series of recurrent acute attacks* with signs and symptoms as described below, usually brought on by sudden strain or exercise. Attacks vary in severity, involve various parts of the body, and occur and persist for varying intervals. The patient usually remains ambulatory.

B. Objective findings:

1. *Swelling of an extremity, or of the scrotal contents is the commonest sign. Extremities.* The swelling is due to a *retograde* lymphangitis. Heat, pain, redness and tenderness are generally present but usually not to a marked degree. *Scrotum:* There is nodular thickening of the cord, known as "funiculitis" and there may be cord-like red streaks. Enlargement of the testicle itself, and the presence of a hydrocele is not uncommon.

2. *Lymphadenopathy is almost always present.* Predominately it is of inguinal, axillary, and epitrochlear involvement, this later being said by some authorities to be very characteristic.

C. Laboratory. There is no specific laboratory test which is generally applicable and reliable for confirmation of diagnosis:

1. *Microfilariae.*—To date microfilariae have been detected in only one or two doubtful instances. Many thousands of searches for the larvae have been made in concentrated blood and in men as long as 21 months after their first symptoms with negative results.

2. *Adult Filaria.*—Adult and degenerative adult worms have been frequently detected in enlarged lymph gland biopsy specimens. The damage resulting from this procedure, however, makes it a *contraindicated* diagnostic test.

3. Complement fixation tests and skin test reactions are of limited value and are still in the experimental stage.

D. Diagnostic exercise test:

1. *Exercise Test.*—Between acute episodes, when physical findings are not present, exercise, particularly of the type that requires heavy exertion, including walking, usually initiates a recurrence. These recurrences frequently are characterized by such typical physical signs as to leave the diagnosis no longer in doubt.

TREATMENT

In treatment the psychological aspects of the problem should not be lost sight of. It has been pointed out that some fantastic worries and erroneous impressions have developed in a number of patients and that there has been fear regarding the transmission of the disease to wives and offspring or that sterility might develop. That these fears are based on unfamiliarity with the facts should be carefully explained. Patients should be transferred from the endemic areas as soon as is practicable and until they are transferred they should be protected from mosquitoes and this is desirable even if microfilariae have not been found in the blood. The prognosis in early cases is usually excellent providing the individual is not exposed to repeated reinfections.

Drugs.—No drug is known to be specific for the treatment of *Wuchereria bancrofti* infection and none that will destroy the parasites during the life of the human host.

Potassium antimony tartrate will sometimes temporarily diminish or remove the microfilariae from the peripheral circulation but they generally return later.

Fouadin (neoantimosan) a trivalent antimony compound, antimony pyrocatechin disulphonate of sodium, which is less poisonous, has a similar but not so powerful a filaricidal effect. Chopra (1936) has tried almost all the pentavalent organic compounds of antimony without any favorable effect. The value of Fouadin in the treatment of *Dirofilaria immitis* infestation in the dog has been studied by Wright and Underwood (1934), Kaw and Cheu (1936), and Johnston (1936). While it has been

demonstrated that Fouadin will destroy the microfilariae in these animals, it frequently will not kill the adults, even when the drugs used later cause the death of the dog. Brown and Austin (1939) have also reported that stibosol, a trivalent antimony compound containing sulphur, might sterilize the blood of dogs. Of 15 dogs treated 3 died. While both of these drugs are certainly inimicable to the existence of microfilariae, it seems evident that the microfilariae in the human body may not be permanently removed by doses of these drugs which are not toxic to the patient.

Anthiomaline has also been used in human cases but only causes temporary diminution in the number of microfilariae.

Brown in recent studies has given 3 cc. intramuscularly at daily intervals for 5–15 injections. Most cases showed a marked diminution in the number of microfilariae shortly after treatment and all cases showed a diminution at the end of 6 months. However, 40% vomited to a greater or lesser extent, some so severely that the drug had to be withdrawn temporarily or the dose decreased.

Culbertson and Rose (1944) have reported that by injections of neostam (stibamine glucoside) they have been able to destroy the adult filarial worm of cotton rats, *Litmosoides carinii* which dwell in the pleural space. However, as noted above, Chopra has tried almost all of the pentavalent organic contributions in man without favorable effect. Solustibosan is the most satisfactory of these drugs, see p. 286.

Owing to the destructive effect on haemolytic streptococci produced by sulfanilamide (prontylin) and its related compound prontosil, and the favorable results reported in the use of these preparations by Nelson and his associates (1938) in the treatment of 347 cases of erysipelas, there was hope that sulfanilamide may prove of value in the treatment of cases of filarial lymphangitis complicated by haemolytic streptococci. In 406 cases of erysipelas at Bellevue Hospital, New York, (1935–6) treated with erysipelas antitoxin, the mortality was in adults 9.2 per cent, in children 37.5 per cent while of 4,473 cases treated (1930–37) with serum, ultra violet rays, X-rays and local treatments with dressings, in adults

and children the mortality was 8.4 per cent. In 347 cases treated in 1938 with sulfanilamide it was but 2.62 per cent. However, the drug may be to some extent toxic and must be used with caution.

Buttle (1939) reports good results have been obtained in a few cases of elephantiasis of filarial origin by the administration of quite small doses of prontosil rubrum, 1.5 grm. daily for 6 days. A rapid subsidence of pain, temperature and swelling followed its use and the condition appeared to be completely cured and there were no records of recurrences.

Ray (1942) who believes that the inflammatory attacks are not due to streptococcal infection but to the adult parasites, emphasizes that sulfanilamide has been effective even when no secondary streptococcal infection is present. For recurrent attacks he suggests induced pyrexia by benign tertian malaria. Ramanamurti (1941) has also advised the use of sulfanilamide but not the induction of malaria for treatment. Earle (1941) has also found striking beneficial results from sulfapyridine for the lymphadenitis complicating filariasis probably due to secondary streptococcal infection.

Since there is no remedy yet known that is effective for the destruction of the filariae, the treatment must be largely symptomatic. For acute lymphangitis, the treatment should consist particularly of rest and elevation of the affected part, healing lotions with mild aperients, and morphia if necessary to relieve pain. Subsequently the extremities should be elevated and firmly bandaged. Since in many cases of filarial lymphangitis there is secondary infection with streptococci or staphylococci, vaccine treatment has been recommended by a number of observers.

Vaccine and Serum Treatment.—Rose, in British Guiana, after preparing autogenous vaccines from streptococci and staphylococci gave these in doses of 100 to 200 millions at fortnightly intervals in 60 cases. He reported that none of the milder cases relapsed, and only 10 of the 19 which had lasted more than a year. Good results were also obtained by Wise and Rose in checking with vaccines the recurring attacks of lymphangitis.

Aubin and Nadessin have employed injections of antistreptococcus lipovaccine in 16 cases of lymphangitis and elephantiasis. They claim that a course of these injections produced rapid and complete improvement in the lymphangitis with fewer and less severe relapses, whether the condition was associated with filariasis or not. There was some shrinking of the elephantoid swelling, and cessation of an existing lymphorrhoea.

O'Connor (1932) has had abundant opportunities to follow up many cases in Puerto Rico, where the patients with filarial lymphangitis have had vaccine treatment and many kinds of injections. He has found that following antistreptococcal vaccine therapy many patients cease to have attacks for from six months to a year, but sooner or later every one of them has further attacks. He has also found that similar relief is equally common following treatment with antiplague serum, antidiphtheritic serum, antitetanic serum, and ordinary T.A.B. vaccine against typhoid fever or used intravenously as protein shock, and he asks whether this result from vaccine treatment may not be a temporary cure from protein shock, rather than an evidence of immunity against specific bacteria.

Grace and Grace (1931) pointed out that streptococcal vaccine therapy was in disfavor at the Public Hospital in Georgetown, British Guiana, though it was difficult to discover a scientific basis for this attitude. They have employed intramuscular or intravenous injections of antistreptococcal serum in the treatment of 47 cases. Six of the cases were given 10 cc. intramuscularly and one, a grave case, 50 cc. intravenously. They attributed the recovery of the very severe case to the use of the serum, and concluded that the use of such serum in lymphangitis was most encouraging, and probably has a place in the treatment of lymphangitis. Ochsner (1934) has reported favorable results in aborting attacks of inflammation in the majority of cases by the use of a polyvalent streptococci serum.

Treatment of Chyluria.—Anderson thought that hexamine and emetine might have some effect. Chopra and Rao reported some decrease in chyluria and lymphangitis after tryparsamide injections. Sherwani (1932) has reported that an intermittent haematochyluria with microfilariae cleared up after ten intramuscular injections

of neostibosan, the dose rising from three-fourths of a grain to 5 grains. However, on the whole drugs usually are apparently of little value in the treatment of this complication. Patients subject to the condition should have rest in bed, laxatives and restriction of fluids and fats. The chyluria is often relieved by avoidance of fat in the diet.

Manson-Bahr (1936) especially advises washing out the bladder with some bland substance such as boric acid, and if there is an admixture of blood, styptics may be added. Chopra (1936) has found that sodium citrate in large doses is of value for the prevention of clotting of the chyle in the bladder.

Golden and O'Connor (1934) have treated 7 cases with roentgen rays applied in the kidney region. While, owing to the short series of cases and the short observation periods (3 months to 3 years), conclusions are tentative, in all of these chyluria ceased for at least the time coincident with treatment.

Surgical Treatment

In elephantiasis of the limbs, much may be done in the early stages by rest and elevation of the affected part and constriction by bandaging and the use of elastic stockings. Massage may also be of assistance. Knott (1938) has found, after experiments with 105 unselected patients with elephantiasis of the legs observed during 10 months, that treatment with pressure bandaging with cotton elastic crepe gave very satisfactory results in many instances. He found that prolonged firm bandaging effects a gradual removal of the lymphoedema in filarial elephantiasis of the leg, the patient gets prompt symptomatic relief from his discomfort, and recurrent attacks of lymphangitis often cease.

When the elephantoid tumors reach a size which greatly inconveniences the patient, operative measures may be undertaken. The most satisfactory procedure in cases of scrotal, breast, or labial elephantiasis, is removal. However, sometimes following removal of the affected part elephantiasis elsewhere, particularly of the legs, may occur.

In elephantiasis of the scrotum it has been stated that the important question involved is the removal of a burdensome mass which, however, is in no way a source of danger to the life of the patient. At the same time, such patients are subject to attacks of elephantoid fever, a condition not without its dangers. There is one factor not usually brought forward and that is the remarkable effect of a successful operation on the mental state of the patient. This is well shown in the accompanying illustrations of the patient before and after operation. If sexual deficiencies are of so powerful an influence on persons of education, how much greater must they weigh on an uneducated native with but few of the higher interests of life.

Prior to operation the patient should be kept in bed for a day or so to lessen the amount of fluid and to secure relaxation of tissues. Thorough scrubbing with soap and water the day of and the day before the operation and the use of alcohol as an antiseptic are important. Some prefer iodine.

For the operation, the lithotomy position is employed. An assistant supports the scrotal tumor wrapped in a sterile towel. Fauntleroy does not recommend a tourniquet to the base of the tumor, as in his opinion it assists but little in controlling haemorrhage and endangers asepsis. Haemostats answer better and as the vessels which give most trouble are deeply situated, the elastic cord would not affect them. In some cases there is very little bleeding. The upper part of the pear-shaped tumor usually affords sufficient sound skin next the thighs for the flaps. As a rule, the elephantoid tissue does not involve the upper 2 or 3 inches of the skin anteriorly, which is thus available to cover in the base of the penis. In addition to this covering for the penis, there is a long prepuce which has been considerably stretched so that after removing all elephantoid tissue

there is enough sound prepuce remaining to cover the distal 2 or 3 inches, so that usually there is sufficient sound skin for a 5-inch penis.

The flaps which are to cover the penis and testicles should be mapped out with shallow incisions and care must be exercised that only sound skin is included in these flaps. Fauntleroy advises a horseshoe shaped incision, commencing at the left side of the base of the tumor about 1 inch from the thigh and about at the level of the penis in health. The incision is carried downward and passes just below the opening of the penis on the tumor surface. A similar incision on the right side completes the horseshoe curve. Next a downward incision in the sound skin is made over the posterior surface of the tumor, thus encircling the base of the scrotum. The anterior horseshoe incision is now deepened to free the penis, care being taken not to injure the spermatic cord. Next the incisions are deepened laterally until the testicles are reached. The

FIG. 302.—Elephantiasis of the scrotum. Before operation. (Fauntleroy.) See Fig. 303.

testicles are usually in the center of the tumor, imbedded in a blubbery tissue from which they can be easily stripped. The remains of the gubernacula are then hooked up and cut close to the testicles. The tunicae vaginales are often thickened and contain fluid which has to be drawn off. In 60 per cent of Fauntleroy's cases it was necessary to remove one testicle on account of extensive disease. One must also bear in mind the possibility of hernial complications and undescended testicle.

A sound is now introduced into the urethra and the septum of the scrotum divided close to the sheath of the penis, then dissecting away the blubbery tissue. At this stage there may be considerable bleeding. The testicles and spermatic cords are then dissected away from the tunicae vaginales. The penis is now freed by a circular incision around and above the opening in the anterior part of the mass. The remainder of the horseshoe flap is now dissected up and the penis freed. The proximal covering for the penis is made from this horseshoe flap which is stitched to the distal one shaped from the prepuce, carefully trimmed of elephantoid tissue. The lateral flaps are brought

together with linen or silk-worm gut sutures, leaving space for a drainage tube, and we thus form a new scrotum for the testicles.

The mortality following amputation of large scrotal tumors does not generally exceed 5 per cent, even in countries where aseptic surgical technic is difficult to obtain. Fauntleroy, who performed 149 such operations in which tumors ranging from 10 to 85 pounds in weight were removed, did not lose a case.

For elephantiasis of the leg an improvement in the surgical treatment has been made by Kondoleon who, by removing long, broad strips of the hyperplastic subcutaneous tissues down to and including the deep fascia in the leg, aimed to establish an anastomosis between the deep and superficial lymphatics. A modification of this operation has been advocated by Auchincloss. The operations necessary are usually performed in successive stages. Auchincloss has made use of the roentgen ray before the operation to disclose areas of extensive fibrosis of the subcutaneous tissue with thickening and obliteration of the vessels and lymphatics, calcification of the filarial worms together with calcification of the blood vessels and the presence of filarial worms deep in the subcutaneous tissue or lying in the deep fascia, thereby removing the diseased tissue and the filarial worms lying in intimate contact with it. Thus, he aims to establish better lymph drainage for the subcutaneous tissue which then lies in direct contact with the muscle.

Bertwistle, Auchincloss, Torgerson and Del Toro have recorded good results from these methods of operation upon elephantiasis of the leg. However, it is only after several years that the real value of the operation can be determined, since after long periods of time the elephantiasis and attacks of lymphangitis may recur.

Abscess should be treated by the usual surgical procedures, such as hot compresses, evacuation, irrigations and antiseptic dressings. As a rule, varicose groin glands (*adenovarix*) should not be operated upon, for the removal of the glands is likely to be followed by elephantiasis of the lower extremities, or irritating lymphorrhoea may result.

Golden and O'Connor (1934) have recommended the roentgen treatment for *lymphangitis and adenitis.* Fifteen cases were so treated. At first merely focal spots were irradiated, but later the entire leg. The impression was gained that larger doses and more prolonged treatment gave better results. Four cases so treated had no further attacks; in two, attacks were as before irradiation; while in some others judgment was difficult.

Recurrent attacks of *filarial orchitis* usually lead eventually to hydrocele. For filarial orchitis with effusion into the tunica vaginalis, Maitland recommends incision into the tunica, turning out any clots that may be found in the sac and stuffing the latter with iodoform gauze.

Lymph scrotum should be supported by a suspensory bandage and protected against the slightest abrasion. It should be kept scrupulously clean and well powdered with talcum. Only if inflammation is of frequent occurrence, with debilitating lymphorrhagia and passes into elephantiasis of the scrotum is surgical removal recommended. In the experience of Manson-Bahr, violent surgical interference with the lymph varices of the scrotum may result in chyluria or elephantiasis of the leg.

PROPHYLAXIS

O'Connor and Beatty (1938), in the study of filariasis in St. Croix, Virgin Islands, where filariasis is very prevalent, found in the examination of 5,000 *Culex fatigans* only 2.3 per cent contained fully developed infective larvae and they concluded for various reasons that less than 1 per cent of *Culex fatigans* in the infested region succeeded in so depositing their larvae as to insure the latter entering their definitive host, man.

Yokagawa (1938) has studied the chances for transmission of *Wuchereria bancrofti* by the intermediate mosquito, *Culex fatigans*. He found that the mature larvae from the mosquito failed to penetrate the normal skin of mice and set up an infection. However, by the application of larvae suspended in saline solution over the broken skin of mice, a limited number succeeded in entering the subcutaneous tissues. Also, when larvae were set free from an infected mosquito during the act of biting, only a few were capable of invading the deeper tissues by way of the orifices left by the bites. (It should be borne in mind that mice are not normal hosts of *W. bancrofti*.) From his experiments,

FIG. 303.—Elephantiasis of the scrotum. After operation. Note change in mental state. (Fauntleroy.) Compare with Fig. 302.

Yokagawa concluded that for infection to take place an orifice by which the larvae may gain an entrance into the tissues should be present, and that there must be sufficient moisture for the larvae to work their way actively into the skin by such an orifice. Hence the chances of the transmission of filariasis by the mosquito is limited by a number of adverse factors which may sometimes explain why the immigration of infected persons into districts infested with mosquitoes which are known to be capable carriers of the parasite of filariasis does not start outbreaks of the infection and such districts are not converted into fresh endemic centers.

Prophylaxis should consist in (1) the destruction of the mosquitoes and their breeding places, especially in the neighborhood of dwelling houses and (2) protection from the bites of mosquitoes. Every carrier of filariasis with microfilariae in the blood is a danger to the community and should be isolated or protected from the bites of mosquitoes, especially at night by a mosquito net.

O'Connor and Beatty (1938) after much study and experience recommended that in areas of high human and mosquito infective incidence the following local measures should be carried out:

1. The nature of filariasis, its transmission and prevention should be completely and simply explained to the occupants of the house where control measures are instituted.

2. Suitable containers for potable and other water supplies should be adequately screened with wire netting. Where containers are not suitable, they should be replaced.

3. The use of the mosquito net should be demonstrated. (If the occupants cannot afford them, these should be provided from public funds.)

4. The proper maintenance and use of all screening should be supervised at intervals by the existing sanitary officers.

5. When possible, occupants should be encouraged to keep fowls in their yards *near* the house, owing to the fact that Culex fatigans is perhaps almost as partial to this kind of blood as it is to human blood and hence fowls may aid in distracting mosquitoes from biting man.

6. The number of mosquitoes in the houses and the percentage of these which are infective should be recorded from time to time in order to evaluate the results of preventive measures.

7. Efforts to have adult mosquitoes killed daily by the inhabitants while highly desirable will usually be found impracticable. This measure would be too expensive for government maintenance, but where full cooperation is assured should be adopted to supplement the foregoing.

Microfilaria Malayi (Wuchereria malayi)

Another sheathed microfilaria of nocturnal periodicity has been described under the name of *Microfilaria malayi* (Brug, 1937). According to Lichtenstein *Microfilaria malayi* differs from *Microfilaria bancrofti* not only morphologically but also biologically. Until 1940 only the microfilariae of this parasite had been described. In that year Rao and Maplestone reported finding the adults from a lymph filled cyst in a patient which showed only *Mf. malayi* in the blood. Chandler noted that these adults were very similar to *Wuchereria bancrofti.* The females as described, were indistinguishable but the male of malayi is reported to differ from bancrofti in such minor details as the number of papillae and the structure of the spicules.

Low (1942) suggests the name of *W. bancrofti malayi* owing to the slight differences. Manson-Bahr points out that *W. pacifica* should not be confused with this species which, he remarks, may be one in evolution which Baylis (1942) prefers to regard for the present as a subspecies.

Bonne, C., and his associates (1941) have also reported the finding of the adult male and female of *W. malayi* in a male Malay patient who died from urosepsis after an operation for vesical calculus. The patient did not show symptoms of filariasis but his blood contained numerous *Microfilariae malayi.* In some enlarged inguinal glands and one popliteal gland at autopsy, one complete male, one complete immature female and a number of parts of mature females were discovered. They closely resembled *W. bancrofti.* The main difference seemed to be the number and shape of the cloacal papillae and folds as indicated already by Rao and Maplestone. Lichtenstein, in 1937, working on the north coast of Sumatra found his attempts to infect various *Culicines* (among them *Culex fatigans*) with microfilariae yielded only negative results, although 320 mosquitoes were examined. This fact, and because no acute forms of filarial disease were encountered in the region, although elephantiasis of the lower leg was common, suggested to him that the filariae might represent a separate species from *Wuchereria bancrofti.* Brug (1927) examined the thick drop specimens of blood sent him by Lichtenstein and found a microfilaria which could be distinguished from *W. bancrofti.* The following characteristics were emphasized for its distinction from *Microfilaria bancrofti:*

(1) The presence of 2 or 3 discrete nuclei in the tip of the tail; (2) in having an anal pore open further anteriorly; (3) in several other minor and, according to Lichtenstein, characteristic differences in length and internal structure.

Faust (1929) examined thick blood smears prepared by Brug and says that the parasite has been so definitely described by Brug as to leave no doubt that it belongs to the family Filariidae and that the specific characteristics given indicate beyond a doubt

that it is a distinct species, probably related to *Wuchereria bancrofti*. Faust gives the following description:

"The larvae measure 220 to 260μ in length by 5 to 6μ greatest in breadth. They are invested with a sheath, which is very much longer than the larvae. The cuticula is very delicately striated. The anterior extremity is bluntly rounded and bears a double stylet process. There are no nuclei in the anterior-most 12 to 16μ. The excretory pore is about 28 per cent distant from the anterior extremity, and the anal pore, about 76 per cent (Brug's corresponding measurements are 28.6 and 77.7). From the region of the anal pore the body decreases to an acuminate caudal extremity. At the extreme caudal termination there is an elongate nucleus and about 10μ in front of this nucleus there is an oval nucleus, the two being much more darkly stained than the other nuclei of the microfilaria. Genital cells (G_1, G_2–G_4) can be seen with difficulty anterior to the anal pore." Faust (1940) says the most distinctive character is the presence of the two discrete nuclei in the tip of the tail.

Feng (1936) has studied the developmental stages of the larvae in the mosquito host. He has found that like *Wuchereria bancrofti* there are 3 true larval stages and 2 ecdyses. He regards the G cells of the larvae as not genital cells but believes they are responsible for the formation of the rectum and the anus.

He has also made a comparative study of the anatomy of *Microfilaria malayi*, *Microfilaria bancrofti*, and *Microfilaria loa*. He points out that *Microfilaria malayi* is structurally near to *Microfilaria loa*, except for its tail. He agrees that *Microfilaria malayi* probably belongs to a distinct species, but until the adults are found this point cannot be definitely settled.

The following table summarizes the differences between *Microfilaria bancrofti*, *Microfilaria malayi* and *Microfilaria loa*.

TABLE OF DIFFERENCES BETWEEN *Microfilaria Bancrofti*, *Mf. Malayi* AND *Mf. Loa*
(Adapted from Feng, 1933)

	Mf. bancrofti	*Mf. malayi*	*Mf. loa*
1	Periodicity usually nocturnal.	Periodicity nocturnal.	Periodicity diurnal.
2	Length: 244 to 296 μ (thick films).	Length: 177 to 230μ (thick films).	Length: 250 to 300μ (thick films).
3	Excretory cell: small (30.75%) near excretory pore (28.95%).	Excretory cell: large (37.07%) far behind excretory pore (30.09%).	Excretory pore: similar (36.6%) to *Mf. malayi* (31.6%).
4	G-cells: small, similar size; G_2–G_4 far behind G_1; G_1 70.14%.	G-cells: larger; G_1 relatively near and larger than G_2–G_4; G_1, 68.33%.	G-cells: similar to *Mf. malay;* G_1, 68.6%.
5	Anal pore: 82.48%.	Anal pore: 82.28%.	Anal pore: 81.9%.
6	Tail: tapering to delicate point; no terminal nuclei.	Tail: swollen at levels of 2 terminal nuclei.	Tail: tapering gradually; caudal nuclei continuous with those of the trunk.
7	Appearance: graceful, sweeping curves.	Appearance: stiff, with secondary kinks.	Appearance: similar to *Mf. malayi*.
8	Pathology: elephantiasis of lymphatics of scrotum as well as extremities.	Pathology: confined mostly to lymphatics of lower extremities.	Pathology: fugitive swelling of subcutaneous tissue.
9	Intermediate hosts: optimum, *Culex fatigans*	Intermediate hosts: *Mansonia* spp., Anopheles spp.	Intermediate hosts: *Chrysops* spp.

Geographical Distribution and Prevalence.—This parasite has not only been reported from Malaya and the East Indies, Sumatra, Borneo, New Guinea, but also from India, especially Travancore, Indo-China, Ceylon, and South China, especially in the region of Huchow. Lichtenstein and Brug first observed the microfilariae in the Celebes, but point out that it is found sporadically in every part of the Indian archipelago.

Brug (1932) pointed out that in the Dutch East Indies *Filaria malayi* is more common than *Filaria bancrofti*. In one locality, 47 per cent of the population harbored *Microfilaria malayi*. In Sumatra, on one estate, 18 per cent were found infected.

Bonne examined 1360 persons at Soekaboemi, Java, and found that 3 harbored *Wuchereria bancrofti* and 7 *Mf. malayi*. Korke also found *Mf. malayi* in Balasore, Orissa, India.

Iyengar (1932) points out that the type of filarial infection occurring in two coastal areas in Travancore has been found to differ from that observed in other parts of India. While both types of filarial infection occur in Travancore, those in the sandy coastal areas resemble *Microfilaria malayi*. In later studies (1938), he reported in 78,763 blood examinations *Mf. malayi* was present in 6138 and *Mf. bancrofti* in 3829, and both parasites in 64.

Dassanayake (1939), in the southern province of Ceylon, found 80 per cent of the filarial infections due to *Mf. malayi* and 20 to *Mf. bancrofti*. Poynton (1938) states that infection with *W. bancrofti* in the Federated Malay States is sporadic apart from Singapore and that the endemic infection is caused by *Mf. malayi*.

Feng found a case of infection with this parasite in Wenchow, Chekiang, China, and suggests that it may be a common infection in this particular province of Chekiang.

Transmission.—Mosquitoes which are known to be intermediate hosts of this filaria include *Mansonioides annulatus*, *M. annulifera*, *Anopheles barbirostris* and *A. hyrcanus* (var. *sinensis*).

With reference to the intermediate host, Brug found that in one locality where 47 per cent of the population harbored *Mf. malayi*, *Culex fatigans* was absent in thousands of mosquitoes caught in the houses there. *Mansonioides annulatus* and *Mansonioides annulipes* were by far the commonest local mosquitoes, and the microfilariae occurred practically only in them. They were found naturally infected in 1.9 and 1.2 per cent. He also found this species acquired experimental infections with *Mf. malayi* to the extent of 83 per cent respectively. All the species of *Mansonioides* are nocturnal feeders. The *Mansonioides* larvae and pupae are found in the water in pady fields in association with *Pistia* plants, on which they depend for air. Iyengar says it is only on the under surface of *Pistia* leaves that the eggs are deposited.

Bonne likewise made attempts to infect *Culex fatigans* with *Filaria malayi*, but failed in the attempt, thus confirming the negative results previously obtained.

Iyengar, working in India, found that this microfilariae did not develop in 800 experimental *Culex fatigens*, but readily did so in *Mansonia annulifera*. In the latter mosquito, natural infection was found in 26 per cent of over 900 specimens.

Jurgens, working in Mamoedjoe in the Celebes, showed that *Anopheles barbirostris* was a good transmitter of this *Filaria*. He was able to infect artificially 83 per cent, while the natural index of infection was 8.9 per cent. In both instances, the larvae were found in the proboscis of the insect. He states that this fairly high infection rate of *Anopheles barbirostris* may account for the density of the infection among the village population (37 per cent), notwithstanding the comparative scarcity of the mosquito.

Mansonioides annulipes, already known as a possible vector, was present in small numbers. A species of *Aedes* (not identified) could not be artificially infected.

Brug (1937) made further studies in Paloe Division, Celebes, and concluded that *Anopheles barbirostris* is probably the most important and indeed only carrier in that region. The natural infection index of this mosquito was 8.1 per cent, about half containing mature larvae. The artificial infection index was 99 per cent. Development of the larvae in this mosquito was complete in 8½ days.

Rodenwaldt (1934), in Java, found *Mansonioides annulifera* was especially infected with this microfilaria—73.6 per cent out of 91 individuals. In other regions, *M. annulatus*, *longipalis*, and *uniformis* are all found infected. Galliard (1939) also believes *M. indicus* is concerned in Indo-China.

Feng (1936) found that complete development in the appropriate mosquito (as, for example, *Anopheles hyrcanus*, var. *sinensus*) required a minimum of only 6 days.

Pathology.—In the Dutch East Indies, Brug states that *Microfilaria malayi* is more often associated with elephantiasis of the legs, and *Wuchereria bancrofti* with elephantiasis of the genitals. Eighty per cent of the infected individuals in one estate in Sumatra suffered with elephantiasis. However, in other parts of the world it is clear that *W. bancrofti* is the species most frequently associated with elephantiasis of the legs.

Korke, in India, also states that *Mf. malayi* appears to be associated with the areas where elephantiasis of the lower extremities is present, while *Mf. bancrofti* seems to prevail particularly in the regions where hydrocele is common. Iyengar found the genital organs rarely infected, but elephantiasis was seen in a child of 6 years.

Galliard (1940) in a study of *Mf. malayi* in the blood during 24 hour periods observed that the maximum and minimum numbers that were found on different occasions at different hours and the total numbers at these same hours were quite variable.

Mansonioides mosquitoes are peculiar in that the aquatic stages develop under water, the larvae and pupae obtaining air by piercing the roots of *Pistia* (water lettuce) plants, less often other aquatic plants. Iyengar has found that the infection can be controlled by destruction of the *Pistia* plants in ponds and swamps. Sweet and Pillai have also reported successful results in the elimination of the infection in North Travancore by destroying *Pistia* and *Mansonioides*.

Dipetalonemiasis (Acanthocheilonemiasis)

Definition.—An infection due to *Dipetalonema perstans*, disseminated in Africa by *Culicoides austeni*.

Geographical Distribution and Prevalence.—The adult parasite was discovered by Daniels in Demerara Indians, British Guiana, and was subsequently described and named by Manson, who also first discovered the microfilaria in the blood of negroes from the Congo in 1891. The microfilaria has been found very commonly in the blood of natives in large districts of tropical Africa, being frequently recorded from the Congo, Nigeria, the Gold and Ivory Coasts and in Sierra Leone. It is common in northern Rhodesia and in Uganda, where in some districts it may be found in 90 per cent of the population. Christie, who made blood examinations in eastern Africa, from the Sudan southward and eastward to Entebbe, found in many areas from 50 to 75 per cent of the

inhabitants infected; 55.7 per cent of infection in the women and 47 per cent in the men; 45 per cent of the children in arms were also found infected. Cases have also been found in Algiers and Tunis.

On the west coast, in the forest portions of the Cameroons, Sharp has found not less than 92 per cent of the inhabitants infected. In west Gabon, Galliard found a wide prevalence, particularly in the native women and children, 45.8 per cent being infected. The degree of infestation, however, varied greatly in the several districts. In certain parts of the forest, the women and children seemed to be immune, while in other parts the blood in 100 per cent showed the microfilariae. As a rule, children between five and twelve years were more frequently infected than adults. On the whole, the most extensive area of infection in Africa is in and around the basin of the Congo. The gorilla and chimpanzee are encountered in some of these regions, and Ziemann and Rodenwaldt and Grigorowa and Nesturch have recorded the finding of this *Filaria* in the chimpanzee, and Reichenow has observed it in the gorilla. The parasite has been reported also from other areas outside of Africa, especially in earlier years in British Guiana and later according to Manson-Bahr probably in New Guinea. It has also been reported from South America, in Venezuela, Trinidad, throughout the lower stretches of the Amazon Valley and in northern Argentine. There appear to be no recent records from the region of British Guiana where the adult worm was first found.

It has frequently been encountered in the blood of Europeans who have resided in central Africa, where it is sometimes found in association with *Microfilaria loa* and *Microfilaria bancrofti* and in South America with *Microfilaria ozzardi*, in the same individual.

Sharp points out that in west Africa, *Filaria perstans*, while common in the natives, must be regarded as one of the rarer parasites of the white man, which he attributes to the fact that the latter invariably uses a mosquito net at night, which is the only time the transmitting agent (*Culicoides*) bites.

Description of Parasite.—*Dipetalonema perstans* (Manson, 1891; Yorke and Maplestone, 1926) (syn., *Acanthocheilonema perstans* (Manson, 1891), Railliet, Henry, and Langeron, 1912) is classified by Yorke and Maplestone in the subfamily SETARIINAE, and in the genus *Dipetalonema* Diesing, 1861, in which the mouth is bounded by lateral epaulette-like structures, the spicules are unequal, and the vulva is in the oesophageal region.

The adult worms are filiform, tapering toward each extremity, especially posteriorly. Near the tip of the tail in each sex there is laterally a pair of short conical processes giving the end of the tail a trifid appearance. The male is smaller than the female, measuring 45 mm. in length by 0.06 mm. in breadth. The diameter of the head is 0.04 mm. Close to the opening of the cloaca there are four pairs of preanal and one pair of postanal papillae. Two unequal, rod-like spicules may be seen protruding from the cloaca. The adult female measures 70 to 80 mm. in length by 0.12 mm. in breadth. The head is club-shaped, and measures 0.07 mm. in diameter. The genital pore opens about 1 mm. from the head. The anus opens at the apex of a papilla situated in the concavity of the curve formed by the tail.

The microfilariae observe no periodicity, being present in the blood both by day and by night, the numbers at different times often varying considerably. Manson-Bahr points out that their special seat of selection is *not* in the peripheral blood, but that of the heart, lungs, aorta, and other large vessels.

They have not been observed in the spleen and only in rare cases in the liver and pancreas. In the blood, the long forms of the microfilariae sometimes measure as high as 200μ in length by 4.5μ in width. They possess in a remarkable degree the power to elongate and to shorten themselves, so that both long and short forms (the latter, predominating, from 90 to 110μ in length and 4μ in breadth) have been recognized.

Microfilaria perstans is in any case much smaller than the microfilaria of *Wuchereria bancrofti* or of *Loa loa*, and is further distinguished by the entire absence of a sheath and by the character of its caudal end, which is invariably truncated and abruptly rounded off. The V-spot is about 30–40μ from the cephalic extremity. There is no marked tail spot and no red-staining granular mass can be demonstrated. It also has a freer and wider motility than the sheathed microfilariae.

Pathology.—The adult parasites have been found particularly in the serous cavities, the mesentery and in the perirenal and retroperitoneal

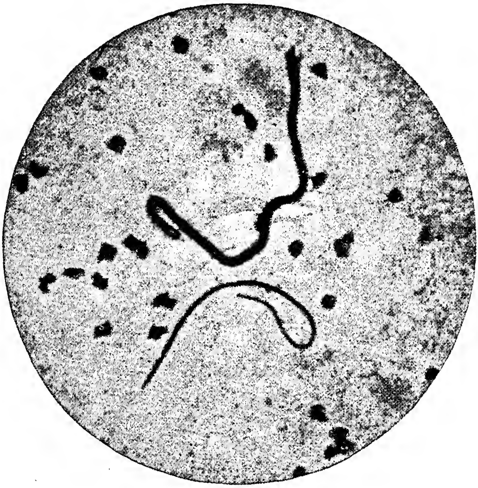

FIG. 304.—*L. oa* above. *Acanthocheilonema perstans* below. (From Green, after Fülleborn.)

connective tissues, and in the pericardial and pleural cavities where they are sometimes found in considerable numbers. Manson-Bahr states that Chesterman has discovered an adult female in a small cyst overlying the brachial artery. Brumpt has reported finding single parasites in the tissues which apparently caused no reaction about them. Rodhain (1937) in one case found the adult parasites under the capsules of the kidney. Numerous investigators have attributed no pathologic significance to infection with *Dipetalonema perstans*, largely on account of the fact that many individuals who harbor the microfilariae of this parasite in the blood, manifested at the time no evidence of disease. However, many cases of infection with *Wuchereria bancrofti* exhibit no evidence of disease.

In wild animals, other species of *Setaria* found in the abdominal cavity are frequently calcified, when they may give rise to moderate inflammatory reactions and to some

adhesions. Faust (1937) states that in a related species, *A. gracile*, found in New World monkeys, the worms characteristically sew themselves into the mesentery, epiploön, pleural lining, and pericardium, where they set up considerable local irritation, with an accompanying fibrinous exudate.

In the past few years there has been an increased amount of evidence relating to the disturbances caused by *Dipetalonema*. Sharp, who has had a very wide experience, states that it is impossible to absolve this nematode from blame as a pathogenic parasite, since there are just as good grounds for assigning to it a share in the production of lymphatic varices of the groin, as there are grounds for designating *Wuchereria bancrofti* as the sole cause of elephantiasis.

Braun and Siefert associate infection with this parasite with oedema, calabar swellings and abscesses. They also state that it may provoke feverish lung affections, and believe that massive infections induce a condition similar to sleeping sickness.

Chambon has noted in a case of sleeping sickness the presence of *Microfilaria perstans* in the cerebrospinal fluid in association with trypanosomes. The microfilariae were also present in the peripheral blood and in lymph from the epitrochlear gland, but not the trypanosomes. He concludes that the meninges were so altered, probably through the action of the trypanosome, that true fissures resulted, permitting the passage of the microfilariae from the circulating blood into the subarachnoid space.

Rodhain has likewise reported calabar swellings or erysipelatous swelling of the feet, which disappeared on rest, in connection with *Dipetalonema perstans*. Fülleborn also attributes the occurrence of calabar swellings to this parasite, and mentions the observations by Marshall concerning the association of oedema in the extremities and other parts of the body, resembling calabar swellings, as being due to *Dipetalonema perstans*. Manson-Bahr says that possibly transient abdominal pains in the region of the gall bladder may be attributed to its presence, and that it may form occasionally subcutaneous cysts.

Morenas has reported a case in which there was toxic oedema of the left eyelid, dyspnoea, precordial pain, and a 50 per cent eosinophilia which was attributed to the infection.

Molser (1939) believes the parasite may in some instances give rise to febrile disturbances (38°–39°C.), since in some cases the fever could be attributed to no other cause, as it disappeared, as did the microfilariae, from the blood after intravenous injections of 1 per cent methylene blue (doses of 2–10 cc.).

Transmission.—Partial development of the parasite had previously been observed in several species of mosquitoes, but none of these could be regarded as true intermediary hosts. The true life history was first demonstrated by Sharp in *Culicoides austeni*, in experiments carried out in the British Cameroons.

If this midge is allowed to bite a man having microfilariae of *Dipetalonema perstans* in the blood, the larvae by the end of 6 hours have passed out of the stomach and are found lying either in the stomach wall itself or in the fat body of the insect. They reach the muscles of the thorax in about 20–30 hours after ingestion, and after undergoing further development they pass to the head and neck of the fly by the 7th day, the cycle in the fly usually occupying from 7–9 days. Eventually the infective form appears in the proboscis of the fly when it has increased to 3 times its original length. The mature larvae escape from the proboscis by stretching and finally bursting the terminal mem-

branous portion of the labium. Seven per cent of the wild flies were found to be infected in the region where the experiments were conducted, where 92 per cent of the natives were infected with the parasite. Only the female bites man. It is a determined night biter, but darkness is not always essential for it to bite. Sharp believes that *Culicoides grahami* will also prove to be a natural carrier of this parasite. Some species of *Culicoides* have been reported to sometimes bite at dusk.

Diagnosis.—Diagnosis depends upon finding the unsheathed microfilaria in the peripheral blood. The parasite must especially be differentiated from *D. ozzardi*. In *D. perstans*, the larvae are usually small and the nuclei extend to the tip of the tail, while in *ozzardi* the nuclei do not extend into the tip of the caudal extremity.

Rodhain and Dubois have applied the intradermal reaction in 3 cases of *Dipetalonema perstans* infection. The injection of the *Dirofilaria immitis* antigen of Fairley, was made into the skin of the anterior surface of the forearm. The 3 patients infected with *Dipetalonema perstans* were said to react in a typical manner, with the appearance of a dermal papule 2 to 3 cm. in diameter, followed by a subcutaneous swelling. In 2 of the cases, the swelling persisted for more than 24 hours, and involved the whole of the forearm. They conclude that the intradermal reaction is applicable to infection with this parasite, and that the reaction is a group one which is applicable at present to infection with all members of the family of the Filariidae.

Treatment.—The treatment for any pathologic conditions produced by *Dipetalonema perstans* is discussed under the treatment of filariasis due to *Wuchereria bancrofti* and under *Loiasis*.

Prophylaxis.—No effective control measures have been discovered. The unfed adult *Culicoides* rapidly pass through 18 mesh screening and mosquito netting, hence only mosquito nets with extremely fine mesh are protective at night. The midges often bite in swarms, usually at dusk. More commonly, they bite only in darkness and protection may often be obtained by having a light near while sleeping beneath the net. They are often found breeding in deep lakes and some species in salt water.

Mansonella Ozzardi

Dipetalonema ozzardi (Manson, 1897; Faust, 1929): Synonyms—*Filaria ozzardi* Manson, 1897; *Filaria demarquayi* Manson, 1897 (*nec* Zune, 1892); *Filaria juncea* Railliet, 1918; *Filaria tucumana* Biglieri and Araoz, 1917, *Mansonella ozzardi*, Faust 1929.

M. ozzardi is known to occur only in the western hemisphere, in parts of Central and South America and the West Indies.

Faust (1929) has created a new genus, *Mansonella* for this parasite, and classifies the genus as a member of the subfamily Setariinae, with the characters of this subfamily, but distinguished by the presence of paired fleshy flaps, lateral to the caudal extremity of the adult female worm, and by unsheathed microfilariae with pointed tails lacking a nuclear core for the terminal 10 to 20μ.

The microfilariae of this parasite were first studied by Manson in blood obtained by Ozzard from Carib Indians from the interior of British Guiana. The microfilaria was at first believed to be different from that obtained by Newsam from the natives of St. Vincent, British West Indies, which was designated by Manson (1897) as *Microfilaria demarquayi*. However, the studies of Penel and of Leiper showed that the two were identical. Faust pointed out that since the name *demarquayi* was used by Zune (1892) for another human microfilaria (possibly *Mf. bancrofti*), it is not available for Manson's species, which becomes *Mansonella ozzardi*.

The common microfilaria of northern Argentine was first described by Biglieri and Araoz. Both these authors and Padilla (1915) considered it a new species, *Microfilaria tucumana*. Later Rosenbusch, and Muhlens (1932) pointed out its resemblance to *M. demarquayi*, and Fulleborn, who has made a careful study of the material from Argentina, found no morphologic differences between *Mf. tucumana* and *Mf. demarquayi*.

Geographical Distribution.—The distribution of this species in the western hemisphere includes British Guiana, Colombia (Balfour, 1921); and in the British West Indies St. Vincent, St. Lucia (Galgey, 1899), and Dominica (Low, 1902); Dutch Guiana (Bonne, 1920); northern Argentine (Araoz and Biglieri, 1914; Bolivia (Muhlens, 1925 and 1932, Vogel, 1927); Yucatan (Hoffman, 1930); Puerto Rico (Hoffman, 1930); Panama (Clark 1930, McCoy 1933); northern South America, Venezuela (Rounti, 1935). The species has been found to be exceedingly common in certain regions of South America. In the Province of Tucuman (Argentina), 50.6 per cent of the inhabitants were found infected, and in the Province of Jejuy, 39.1 per cent (Muhlens, 1932). Padilla found the rate of infection in some instances to vary between 16 and 25 per cent. McCoy (1933) found that the blood of 44.5 per cent of 119 Indians examined in Darien Province, Panama, contained this parasite. The infection rate in native villages in the same region varied from 2 to 57 per cent, and averaged 9.9 per cent in the 244 natives examined. Although this species was reported by Manson and by Seligmann as occurring in New Guinea, it seems now possible that the species may be instead *Microfilaria malayi*, which has been especially encountered in the Celibes.

The Parasite.—The adult females of *Mansonella ozzardi* have been studied by Galgey, Daniels, Low and Ozzard. The adults have apparently not yet been recovered from any of the cases in northern Argentine.

The adult male is known only from a single posterior fragment of 38 mm. The tail is strongly recurved and becomes gradually narrowed up to 0.27 mm. from the tip, where it abruptly rounds off into a slightly bulbous termination.

The female worm has a length of 65 to 81 mm. and a maximum breadth of 0.21 to 0.25 mm. The cuticula is smooth; the head is unarmed. The small mouth leads directly into the oesophagus. The anal opening is on the summit of a small papilla 0.25 mm. from the posterior extremity. On either side of the caudal extremity there is one pair of lappets with a fleshy core. The vulva is situated 0.71 to 0.76 mm. from the anterior end of the female worm. The small oval eggs measure $21 \times 8.4\mu$. The microfilariae are unsheathed and are very active in fresh blood films. They are much smaller than *M. bancrofti* and are characterized by a sharp pointed tail free of nuclei at the tip. Usually they measure about 200 by 5μ. The location of the various points of identification in relation to the total body length of the larva is given by Vogel as follows:

	Per Cent
Beginning of the first head nuclei	2.5
Nerve ring	21.9
Excretory pore	31.5
Excretory cell	35.0
G_1 cell	69.3
G_4 cell	79.2
Anal pore	79.4
End of the last tail nuclei	98.0

McCoy found that the microfilariae observed by him in Panama in 1933 corresponded in general to these morphologic details given by Vogel. *M. ozzardi* is said to observe no periodicity.

Transmission.—Low found some development stages of *M. ozzardi* in *Aëdes aegypti*. Davis (1928) fed 117 mosquitoes on a carrier of *M. ozzardi* in Argentina. Of these, 4 were found infected (2 *Anopheles tarsimaculatus*, 1 *Anopheles olbitarsis*, and 1 *Aëdes aegypti*). In each case the thorac muscles were involved. The head and probosces were not invaded. He thought that *Anopheles tarsimaculatus* and possibly *Anopheles albitarsis* might be the responsible transmitters. Owing to the fact that the disease

prevails in wooded areas near streams, particularly in the foothill country, he suggests that a further study should be made of other insects, especially of *Simulium*.

Buckley (1934), working in St. Vincent, British West Indies, has conclusively demonstrated the development of *F. ozzardi* in the sand-fly *Culicoides furens* Poey. Two hundred sand-flies collected in the vicinity were given an infective feed of blood of *F. ozzardi* carriers.

Of these flies, 27.5 per cent were subsequently found to be infected with developing stages of the parasite. The ingested microfilariae migrated within twenty-four hours to the thorax, where the entire morphologic development takes place. In flies which were kept alive for 7 or 8 days, advanced stages were found in the thorax and head, and their emergence from the proboscis was induced by light pressure on the head. Five per cent of *Culicoides furens* caught in the vicinity were found to be naturally nfected with developing larvae.

Pathology.—Daniels (1899) found the adult parasites at the autopsy of 2 Demerara Indians. They were situated in the mesentery and the visceral fat. Later Galgey found 5 adult females in the omental tissues of a native of St. Lucia. As is generally the case with other species of Setariinae found in animals, the adult parasites give rise to no pathologic lesions, except when they become cretified, when slight inflammatory changes may occur about them. The worms generally are regarded as non-pathogenic.

Muhlens (1932) states that while in general individuals inflicted with these microfilariae in Argentine were generally without manifest clinical symptoms, nevertheless, most of them showed some anaemia and a yellowish or slightly blue oedematous complexion. Perez regarded this condition as characteristic of the infection. It was, however, difficult for Muhlens to interpret these signs, in view of the fact that the individuals usually suffer with malaria or ankylostomiasis, or even nephritis. Muhlens also states that the infective cases occurred almost exclusively among the poorer classes who live in miserable shacks in wooded areas of the country.

McCoy, in Panama, states that none of the individuals infected showed any obvious symptoms which could be ascribed to the filarial infection.

Loiasis

Definition.—Loiasis is a form of filariasis caused by *Loa loa;* the parasite frequently produces no symptoms of disease, but in other instances gives rise to inflammatory processes and to fugitive swellings of the skin, probably of allergic origin (calabar swellings). It is transmitted by *Crysops dimidiata* and *C. silacea*.

Geographical Distribution.—*Loa loa* (*Filaria loa, Filaria oculi, Filaria diurna*) is widely distributed in west and central Africa, and particularly along the Congo River and its tributaries.

It is found on the west coast from Sierra Leone to Benguella, confined mostly to the coastal plains and the delta regions. It is especially common in the Cameroons, Calabar, and along the Ogowe River, where a very high rate of infection has been found. Brumpt (1904) found 15 per cent of the inhabitants along the Welle River infected. Low remarked that it is no exaggeration to say that if Europeans reside for more than 5 years in the regions of Niangara and Nala in the Haut Welle Province and Ibambi in the Iturbi Province in central Africa, they are certain to become infected. Woodman and Bokhari (1941) report 15% of the population of the Anglo-Egyptian Sudan infected.

History.—*Loa loa* was early known as the eye worm of Africa, its occurrence was perhaps observed and first pictorially represented by Pigafetta during his travels along the Congo River in 1598. The earliest record of the removal of the parasite was that of Mongin (1770) who extracted it from between the conjunctiva and albuginea of a Negress at Santo Domingo, Haiti.

Shortly afterwards a number of other cases were reported from French Guiana, Santo Domingo and Brazil, all, however, in recently imported West African slaves. The first report of the parasite in Africa was by Guyot (1778) in Angola, where infection was found to be common and the parasite described under the native term "loa." In the United States, cases have been reported from time to time. Ward, who collected from the literature 97 cases of infection, also studied cases occurring in this country up to 1906, and wrote an excellent monograph upon the subject, and Smith and Rivas (1914) and Kimberlin (1923) described other cases. Kimberlin points out that the parasite has not infrequently been extracted from the eye in the United States. All the cases which have been reported from the New World are now generally believed to have contracted the infection in the endemic areas in Africa.

FIG. 305.—*L. loa* in the subcutaneous tissues, twice normal size. (After Fülleborn.)

Etiology.—Apparently all races are susceptible. Adults are more commonly found infected than children. Males and females appear to be almost equally infected.

Description of Parasite.—*Loa loa* (Guyot, 1778) is classified in the subfamily of Loainae (Yorke and Maplestone, 1926) and in the genus *Loa* Stiles 1905, in which genus the spicules are unequal and dissimilar. *Loa loa* is the type species.

The adult male measures about 30 to 34 mm. in length and 0.3 to 0.4 mm. in greatest thickness. The female is about 50 to 60 mm. in length, with a maximum breadth of 0.5 mm. Hence it is shorter but somewhat thicker than *Wuchereria bancrofti.* The body is cylindrical, filiform and tapering anteriorly to the small mouth which is simple and without lips. The truncated head is provided with two lateral and four small submedian papillae. The cuticle is not striated, but is characterized by the presence of numerous rounded small bosses, except at the anterior extremities of both sexes, and at the tail of the male. The mouth opens directly into the slender oesophagus, followed by a long filiform intestine, ending in a short rectum. The tail of the male is bent spirally. Caudal alae are sometimes visible. There are five pairs of large, pedunculated papillae with about three pairs of small, sessile papillae towards the caudal tip. The spicules are unequal, measuring 123 to 176μ and 88 to 113μ, respectively. In the female, the posterior extremity is rounded, with a pair of papillae near the tip. The vulva is situated behind the oesophagus, some 2.5 mm. from the anterior end. The uterus contains all stages of the developing embryos which are enclosed in the covering membrane, and which, as in the case of *Microfilaria bancrofti*, becomes elongated when the parasites are born. The microfilariae are found generally in the blood during the daytime and not at night, hence the original designation by Manson of *Microfilaria diurna.* However, Sharp (1923) found in northern Nigeria that in no case observed was there strict diurnal periodicity.

Microfilaria loa (Fig. 304) is very similar in size to *Microfilaria bancrofti*, measuring on an average of about 290μ in length by 7.5μ in width, and likewise enclosed within a sheath. Its tail is pointed and it has similar V-shaped and tail spots. Certain points

of differentiation have been described in stained preparations of both living and fixed parasites, especially by Sharp and by Fülleborn. In stained preparations the larvae can usually be distinguished by the fact that in *Loa loa* they show angular curves and an acute bend at the tail. Another point suggested for differentiation is the character of the column of nuclei, which in *Microfilaria loa* reaches to the tip of the tail, and is separated from the cuticle by a definite space. The nuclei are usually coarser and end squarely at the head, instead of in a curve. In *Loa* also the V-shaped spot appears in stained specimens as a hollow viscus with a chromatin-staining body on its outer side. The nuclei of its cuticular cells can easily be distinguished when stained with dilute Giemsa solution, whereas in *Microfilaria bancrofti* they are never seen discretely. *Mf. loa*, however, never exhibits the red granular mass ("Ipperkörper") of Fulleborn, seen as a series of discrete nuclei on a blue background in *Mf. bancrofti*. It has been pointed out that the developing larvae may closely resemble those of *W. bancrofti*. In intra vitam staining with methylene blue (1–5000), *Loa loa* begins to take up the stain in 10 minutes, while in the case of *Microfilaria bancrofti*, absorption is much slower and the stain shows an affinity for the excretory pore

Transmission.—Manson (1895) called attention to the mango fly, *Chrysops dimidiata*, as a possible intermediary, on account of its diurnal and blood-sucking habits and local distribution. Leiper, in 1913, in Nigeria, first carried out experiments with *C. dimidiata* and *C. silacea*, and observed developmental changes of the parasite in these flies, and involvement of the salivary glands. Kleine (1915) in the Cameroons, examined 500 *Crysops dimidiata* and 100 *C. silacea*, and found that 32 (5 per cent) were infected and that in 9 (1.5 per cent) the larvae were fully matured.

The more complete life cycle of *Loa loa* was elucidated by Connal and Connal in Nigeria, in 1921–22.

They also found these flies naturally infected with microfilariae. Later they succeeded in infecting wild flies of these two species (*Crysops dimidiata* and *C. silacea*) with the microfilariae of *Loa loa* from man. The development of the microfilariae in the fly is similar in many respects to that of *Microfilaria bancrofti* in the mosquito. After the development in the thoracic muscles and fat body, the larvae migrate towards the head, where the mature ones, measuring about 2 mm. in length by 25 μ in breadth, are found in largest numbers about the tenth day. When they are ready to leave the fly at the time that it bites, they make their way through the labium. Most of the mature larvae leave the fly on about the tenth day. The fly, however, may remain infective for an additional period of about 5 days. Within a minute after the worms have emerged from the fly, they have disappeared under the skin, as was demonstrated by experiments upon guinea-pigs. However, attempts to establish infection in monkeys, rabbits and guinea-pigs did not result successfully. After penetrating the skin, the microfilariae apparently pass to the subcutaneous tissues. Nothing further is known of the development of the parasite in man.

In connection with the fact that the microfilariae of *Loa loa* are found in the peripheral circulation of man usually only during the day, it may be of interest to recall that *Chrysops* is a strictly diurnal biter. From sunrise until 10 or 11 a.m., and from 4 p.m. until dark are the periods when the fly is most numerous and active. It seldom bites in bright sunlight, preferring the shade of the trees and the shelter of the veranda. Only the female bites and transmits the disease in man.

The development of the parasite in human beings is apparently usually very slow. In a number of cases, the presence of the parasite was not discovered until 3 or 4 years after the individual had left the endemic area.

Hauer (1932) reports one instance in which the first skin symptoms suggestive of *Loa* infection occurred 3 years after he first reached, and 1½ months after he finally left, an endemic area. The shortest period on record is apparently one reported by Elliot, who noticed the presence of the parasite in and about the eyes within a year of the arrival of the individual in an endemic center of infection.

In 2 cases, a parasite was extracted from the eye 9 and 13 years, respectively, after the patients had left Africa. In another case the worms appeared at intervals during 15 years. In an instance reported by Knabe where infection was acquired in the Cameroons and in which *A. perstans* was also present, infection persisted in Germany from 1915 to 1930. Laveran suggested that the life span of *Loa loa* was 14 years. Manson-Bahr reports a case in which all signs of the adult worms and traces of the microfilariae had disappeared after a duration of 17 years.

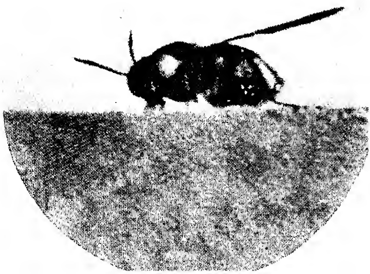

FIG. 306.—Chrysops in act of biting. (After Conal.)

Another fact suggestive of the slow growth of the parasite is that while the immature active worms are sometimes seen beneath the skin in children, the microfilariae are rarely found except in adults, and in one case not for 7 years from the supposed time of the original infection.

With reference to this point, Manson-Bahr has reported a case in a British officer in which calabar swellings were first noted in 1916 in Africa. He returned to England in 1917. An adult filaria appeared in the left eye in 1919. The blood was repeatedly examined for microfilariae during the subsequent years, with negative results. In 1922, microfilariae were found for the first time. Therefore, in this case, an interval of 6½ years elapsed before the appearance of the larvae in the peripheral blood. Manson-Bahr, however, does not suggest that such a long period elapsed before the adult worms attained maturity, but that the embryos had for some reason been prevented from entering the blood stream.

Pathology.—The habits of *Loa loa* are quite different from those of *Wuchereria bancrofti*. Not only do the *Microfilaria loa* occur in the blood in the daytime rather than at night, but the adults, instead of remaining in one locality and blocking the lymphatics, usually circulate about the connective tissue and appear beneath the skin in various parts of the body. Also, *Loa loa* is more especially a parasite of connective tissue rather than of the lymphatic glands. The adult worms have been found particularly in the connective tissue in many different parts of the body, as, for example, the subcutaneous tissue, often under the muscular aponeurosis of the extensor surface of the arms, legs, fingers and trunk, and on the surface of the organs in the mesentery, under the parietal peritoneum and pericardium, sometimes about the genital organs. They have also been found encysted in the heart muscle and in the anterior chamber of the eye, under the ocular and palpebral conjunctiva, over the bridge of the nose, and in the frenum of the tongue. Brumpt found in one necropsy, in

the tissue of the heart, 5 adult parasites, 4 of which were dead and cretified and one of which was living.

Klotz has described the pathologic changes which may result from the presence of *Microfilaria loa*, as observed in the spleen of two African natives. *Microfilaria loa* was found in the blood of one before death. On section the spleens were studied with pin-point yellowish nodules. Histologically there was a diffuse fibrosis becoming denser in some areas. The malpighian bodies were small and many had apparently disappeared, the lymphocytes being sparce and largely replaced by endothelial cells with fibrosis along the sinus walls. In other areas the whole splenic architecture was obliterated by nodular masses of fibrosis in which eosinophils were the predominant wandering cells. Remnants of the sinuses could still be traced through these fibrosed areas and within these blood channels many well-stained *Microfilaria loa* were encountered. About groups of these microfilariae an inflammatory reaction and fibrosis were present. Klotz suggests that these reactions in the spleen may be analogous to the pathologic condition which occurs in chronic calabar swellings. He emphasized (in connection with his study of other cases infected with *Loa loa*) that it is evident that the temporary resting of the microfilariae within the visceral capillaries is unaccompanied by tissue reaction, while a more permanent abode of them, as seen in the spleen, is associated with inflammation and fibrosis.

The production of inflammatory processes, the oedema, the cyst-like swellings and the transient tumors which result during the course of infection are discussed under the clinical features (see below).

Clinical Features and Symptoms.—During life the filaria may sometimes be noticed beneath the skin of the fingers or in different parts of the trunk. Sometimes it seeks soft loose skin, as of the breast, the lingual frenum, the region of the epiglottis, the skin of the penis, the eyelids and conjunctivae, and the anterior chamber of the eye. Chesterman, in Yakusu, Africa, reports finding live adult worms in 10 per cent of the cases he operated on for hernia, elephantiasis, etc. Parasites were particularly found in the inguinal scrotal regions. In one case he found 40 living worms around the cord. From the frequency that the worm has been observed in the region of the eye, it would appear that the parasite has a special predilection for that region. However, Brumpt points out that he did not see the worm once in the eye in the hundreds of *Loa loa* cases examined by him. Worms are also very common in the region of the nose.

The adult parasites seem to be sensitive to different temperatures and are often attracted to the surface of the body by the warmth of a fire or by fomentations applied to the skin, and on exposure to cold the worm may pass into the depth of the eyeball. When the parasite appears under the conjunctivae, it may cause a considerable amount of irritation and congestion, also great pain and swelling in the lids, giving rise to redness and at times lacrimation. Also pain and swelling in the cheek may accompany the movements of the parasite near the eye. The

combination of itching, pain and irritation caused by the movements of the parasite under the conjunctiva is described as simply maddening by Elliot in his book on "Tropical Opthalmology." However, almost instant relief is obtained when the parasite moves into the deeper tissues. In an instance reported by him with the parasite in the region of the ear, the patient suffered on a number of occasions from an intense neuralgia behind, below and in front of the ear. This was accompanied by great hyperesthesia of the superjacent skin. Great pain is also sometimes experienced by the presence of the worm in the region of the posterior

FIG. 307.—Photomicrograph of section of cystic tumor produced by *Loa loa*. (Harvard African Expedition—1930.)

urethra and neck of the bladder. Serious consequences might result from its appearance in the region of the rima glottidis or in the urethra.

Frequently the migrations of the adult parasites give rise to no serious inconvenience, though in their progress beneath the skin they may cause creeping and prickling sensations, itching and sometimes oedematous swellings in various parts of the body, known as calabar swellings.

Calabar Swellings.—These are transient tumors, usually about the size of a small hen's egg. They originate suddenly, sometimes preceded by sharp pains, and may remain for about three days before disappearing slowly. They occasionally may last for a week or longer. Sharp reports one instance of their persisting for 61 days. They may occur subcutaneously in any part of the body. Frequently they are seen about the wrist or arm. As many as half a dozen may appear in the course of a month.

The swelling may be painful or painless. The skin over it often itches. At times the swelling has been noted to move its position to the extent of several inches an hour. The transient tumors do not suppurate. Usually an eosinophilia is present, sometimes as high as 50 to 70 per cent. Microfilariae are often absent from the blood, but they may be observed in serum withdrawn from the area of the swelling. When the swellings repeatedly recur on the arm or leg they may give rise to permanent cyst-like swellings (chronic calabar swellings) which have been described by Low and Manson-Bahr. Manson-Bahr notes that in such instances there is induration of the fascia and of the connective tissue in the vicinity of the tendon sheaths which may cause pain on muscular movement. Apparently these swellings are attached to the tendon sheaths and muscular aponeuroses.

In a Congo native, the Harvard-African Expedition (1930) found a small cystic tumor, measuring about 5 cm. in diameter, on the right arm, about 6 cm. above the elbow. The tumor contained straw-colored fluid, and an adult *Loa loa*. Sections of the tumor showed a dilatation of a gland-like cavity of which the fibers of the surrounding tissue had been pressed apart by the movements of the parasite and the slowly accumulating fluid.

There has been much speculation as to how the transitory "calabar swellings" are produced. It has been suggested that they may be due to the wanderings of the parasite, or to the birth and discharge of a large number of microfilariae from the adult female, as puncture of the swellings has sometimes shown numerous microfilariae in the oedematous fluid. It was also suggested by Ward that they may originate from some toxic excretion of the parasite. Low, Caro, and O'Connor also emphasized the idea of an association between these swellings and toxin production. Fulleborn suggested that they represented evidence of a host reaction to *Loa* antigen, an anaphylactic phenomenon.

Chandler and his colleagues (1930) have produced a typical calabar swelling in a patient infected with *Loa loa* by the injection of a *Dirofilaria* antigen.

Within 20 minutes after the injection, there developed a circumscribed, red, itchy, oedematous swelling about half the size of a hen's egg, which was of precisely the same nature as the calabar swellings which the patient had previously experienced. By the end of an hour, it covered an oval area about 3×6 cm. in diameter. From 12 to 24 hours later, the swelling and inflammation continued to spread, so that approximately two-thirds of the under side of the arm was involved. They concluded that in this case the injection of the *Dirofilaria* antigen had set up a specific allergic reaction in the skin which had been sensitized by the presence of a *Loa* infection.

Fulleborn and Sonnenschein, who had previously failed in producing calabar swellings by the injection of a *Loa* antigen, finally succeeded in producing two calabar swellings in a patient infected by *Loa loa* by the intracutaneous injection into the arm of a *Dirofilaria immitis* extract.

Fairley after a study of skin tests in loiasis was convinced that the calabar swellings essentially arise from a local anaphylactoid reaction involving the cells of the subcutaneous tissues, not primarily of the dermis. He suggests that the reaction is analogous in many respects

to the delayed reactions so frequently met with on injecting saline extracts of helminths into the tissues.

Occasional Symptoms.—In addition to the itching and prickling sensations and a feeling of tension which the worm sometimes causes when it appears in the subcutaneous tissues, the course of the parasite may be marked by an oedematous track; in other instances, by diffuse oedema of the back of the hands and of the forearms (Meinkof). Redness of the skin has very rarely been noted. Fairley states that a generalized urticaria sometimes occurs. Stitt reports a case in a physician in which the first symptoms were transient painless swellings about the joints, associated with stiffness. Various diagnoses, such as rheumatism, erythema nodosum and angioneurotic oedema were first made in this case. Inflammatory swellings, nodules, both in muscular and connective tissue (Ziemann), and mutiple intramuscular abscesses due to staphylococci or streptococci, and even purulent infection of the hip joint (Manson-Bahr) may be sometimes found in association with *Loa loa.* Chesterman in one instance found a definite lymphatic stone in the scrotum of a case of elephantiasis which showed calcified *Loa loa* in the center. Woodman and Bokhari (1941) have reported the enlargement of lymph nodes with chronic fibrosis that were believed to be caused by *Loa loa* in the Sudan. They say it was common to find *L. loa* moving about especially among the blood and lymphatic vessels of the cord, and three times one was found in a lymphatic varix.

Diagnosis.—Connal (1934) has studied 115 cases of calabar swelling in individuals resident in Nigeria, 30 of whom were Europeans. He states that the four signs of infection with *Loa loa* in the order of their frequency in the 30 Europeans were (1) calabar swellings; (2) visits of the worm to the eye; (3) outline of the worm beneath the skin; and (4) microfilariae in the peripheral blood. Puncture of the swellings sometimes reveals large numbers of microfilariae in the oedematous fluid. The eosinophilia is usually marked. The microfilariae are diurnal and often most numerous in the peripheral blood about mid-day. Points of differential diagnosis have already been considered on p. 1333. Eosinophilia has been emphasized as a help in suggesting diagnosis. Hauer (1932) found it of assistance in his 2 cases in which the eosinophilia was between 75 and 78 per cent. High eosinophilia, however, may also occur in infections with other FILARIOIDEA, as in *Dracunculus medinensis*.

With reference to diagnosis by the cutaneous reaction and complement deflection test, Fairley has found with *Dirofilaria immitis* antigen that both these tests were strongly positive in 6 cases of *Loa loa* infestation. He admits, however, that more information must be acquired regarding the specificity of the reaction, and it may yet prove that a negative result is of more value in excluding filariasis than a positive reaction is in indicating it. While the complement fixation reaction with *Dirofilaria immitis* antigen, he found, "is almost always strongly positive in *Loa loa* infestation, it has yielded disappointing results in a considerable number of sera collected in India from patients showing microfilariae. Only 5 out of 23 cases yielded positive results." He concluded that "*Dirofilaria* extract, therefore, cannot be regarded as a satisfactory antigen for detecting circulatory antibody in filariasis."

Rodhain and Dubois have also performed intradermal injections of 0.25, 0.2 and 0.1 cc. of Fairley's 0.5 per cent *Dirofilaria* antigen. In 6 cases of *Loa* infection, a typical positive immediate reaction followed. Of 15 controls, one gave a pseudoreaction, the wheal reaching 2.7 cm. in diameter. Low and Connal (1934) both recommend the skin test of Fairley as an aid in diagnosis.

Treatment.—In cases where the worms reach the surface, as for example the conjunctiva, they should if possible be removed through a small incision. It is necessary, however, to seize the parasite securely with forceps before cutting down to it, as otherwise the parasite may escape and disappointment is apt to ensue.

Elliot points out that the principal difficulty in removing the parasite from the region of the eye arises from the irregularity with which the worm visits the skin surface and the rapidity with which it leaves it when alarmed and disturbed. The patient may feel it in the neighborhood of the eye and hurry to the surgeon only to find that in the interval it has disappeared. Again he may actually arrive with the parasite under the conjunctiva or in the lids and yet his haste may be fruitless owing to the parasite moving quickly into the deep tissues as soon as the surgeon attempts an examination. Hence, everything that is required for operation must be in readiness. If the worm is seen, a solution of cocain combined with adrenalin should be carefully instilled. If the worm attempts to escape, it should be seized through the conjunctiva with fixation forceps. A silk suture should then be passed under the worm and tied sufficiently tight to prevent its escape. The removal of the parasite is effected by making a snip in the conjunctiva over the worm, and the worm gently withdrawn with forceps. The conjunctiva wound is then closed, a suture being inserted if need be. Should the parasite disappear before it can be seized, it may often be brought to the surface again by the aid of hot fomentations. For the intense pain which the parasite sometimes causes in the region of the eye, Elliot recommends the instillation of a solution of novocaine into the conjunctival sac, which brings about a speedy relief of the suffering. If the parasite is under the conjunctiva, novocaine solution should be used for local anaesthesia.

The treatment of calabar swellings consists in the application of cooling lotions to allay the irritation. Chandler, Milliken, Schuhardt, have found that the injection of 2 minims of adrenalin causes the itching to disappear within one-half hour and the turgidity and heat of the calabar swellings to decrease markedly. Manson-Bahr recommends for the urticaria and pruritus which is sometimes troublesome, a 10 per cent alcoholic solution of heliobron (dibromotannic urea) applied to the skin at night. In a few instances, injections of tartar emetic have been reported of value in the treatment of the calabar swellings. Others have recommended intravenous injections of anthiomaline in doses of 3 cc. of a 6 per cent solution every other day.

Loa Inquirenda.—A new species of the genus *Loa*, *Loa inquirenda*, has recently been found by Maplestone (1938), 2 unfertilized female *Filariae* being removed by Rishworth from a European resident in *India*. Maplestone found the parasite clearly unlike *F. bancrofti*. It resembled *Loa loa* in that it has bosses on the cuticle and it is 2 or 3 times as long, 13 to 14 cm. in length, whereas the adult female *Loa* is not over 5 or 6 cm. Moreover, its posterior extremity is straight and the anus is subterminal. There were no microfilariae in the blood, hence, Maplestone emphasizes, it cannot be the adult of *Microfilaria malayi*.

Prevention should consist in protection from the bites of *Chrysops* flies in the endemic areas. No really successful larvicidal measures against the fly have been developed. Films of kerosene or semi-refined fuel oil placed on the surface of pools over which the flies skim are sometimes destructive.

Key to Filarial Larvae

I. Present in peripheral blood.
  A. Sheath present.
    1. Nocturnal periodicity (usually).
      a. Tail pointed, straight, no nuclei in tip. Sheath moderately prolonged beyond tail. Break in cells 50μ and V-spot 90μ from head. Graceful curves. Lashing movements. Size 300 by 7.5μ. . . . . *W. bancrofti*.

b. Tail pointed, straight; an elongated nucleus in tip. Sheath much prolonged beyond the tail. No nuclei at anterior end. Size 250 by 5 to 6μ. *F. malayi*.

2. Diurnal periodicity.

a. Tail pointed, sharply flexed; nuclei coarse, extending to tip. Sheath moderately prolonged beyond tail. Break in cells 40μ and V-spot 60 to 70μ from head. Irregular sharp flexures. Size 250 to 300 by 7.0μ. *Loa loa*.

B. Sheath absent. No periodicity.

1. Tail sharp, straight; nuclei not reaching tip. Size 200μ by 5μ...*M. ozzardi*.
2. Tail blunt, straight; nuclei reaching tip. Break in cells 34μ and V-spot 50μ from head. Lashing progressive movements. Size 200μ by 4.5μ (variable). *A. perstans*.

II. Present in lymph spaces, not in blood. (No sheath, no periodicity.)

1. Tail sharply pointed, end gracefully curved; nuclei do not reach tip. V-spot 60μ from head. Size 300μ by 8μ..........................*O. volvulus*.
2. Tail blunt, end curved like handle of cane; containing a single row of round nuclei which reach the tip. Size 200μ by 5μ................*A. streptocerca*.

Onchocerciasis

Definition.—The term onchocerciasis implies a parasitic infection with the nematode *Onchocerca volvulus*, in which the most characteristic clinical manifestation is the occurrence of subcutaneous nodules or tumors. In certain individuals who apparently show special sensitiveness to the presence of the parasites, or to the action of their toxins, products of metabolism, or disintegration, secondary disturbances of the skin and eyes may occur.

In the eyes, the lesions sometimes result in disturbances of vision and blindness, and hence in Central America the affection is frequently referred to as the "*blinding filarial disease*," and the parasite which causes it as *Onchocerca caecutiens*.

The infection is transmitted by at least five species of flies of the genus Simulium; *Simulium damnosum*, *Simulium avidum*, (syn. *Simulium metallicum*), *Simulium ochraceum*, *Simulium mooseri* (syn. *Simulium callidum*) and *Simulium neavei*, which are indigenous to the various countries in which the affection occurs.

History.—The African condition was observed originally by a German medical missionary, who found worms in the tumors of two negroes of the Gold Coast Colony. Leuckart, who examined this material, studied and named the parasite in 1893, *Filaria volvulus* (*Onchocerca volvulus*). Prout (1901) observed two cases in Sierra Leone, and Brumpt (1904) found 15 cases in natives in Central Africa along the Welle River. Later the disease became widely known in Africa and has been studied especially by Fulleborn in the Cameroons, by Rodhain and Hissette in the Belgian Congo, by Dyce Sharp in Nigeria, by Blacklock in Sierra Leone, and by the writer in Liberia and the Belgian Congo.

In 1915 Robles first observed this condition in Guatemala. Upon removing a tumor from the head of a child he recognized its parasitic nature. In 1916, at a conference of physicians in Guatemala and in 1919, before the Société de Pathologie Exotique, Paris, he gave a detailed account of the condition and showed that it was caused by a species of *Filaria*. He also emphasized that the nodules about the scalp often were associated with disturbances of the eyes, and that these disappeared following removal of the tumors. He also described, in connection with the disease, a definite and specific type of erysipelas, *erisipela de la costa*. Subsequently Luna and Calderon confirmed

these observations and reported upon the favorable results obtained by the removal of the tumors. More recently the disease has been studied clinically, etiologically and pathologically in Central America by Larumbe, Hoffmann, Ochoterena, the writer and others.

Brumpt in 1919 studied parasitic material sent to him by Robles consisting of one male parasite and fragments of the extremities of two females. He reported that, while the Guatemalan parasite was morphologically almost identical with the species of *Onchocerca volvulus* found in subcutaneous nodules in Africa, it differed especially in the size and distribution of the papillæ in the male parasites and by the greater size of the spicules. For this reason and also because of the data known then regarding different geographical distribution, differences in the location of the tumors in the patients in Africa and in Guatemala, as well as on account of different pathological manifestations observed in Africa and Guatemala, he separated it as a new species, calling it *Onchocerca caecutiens* or the "blinding filaria."

Subsequent work carried out by Fülleborn (1924, 1926) and by Sandground (1933), in which a large number of parasites were studied, has shown that, while there may be considerable variation in individual specimens, there are no constant morphological differences between the African and the Guatemalan human parasites, and that, hence from a morphological standpoint, it is doubtful if *Onchocerca caecutiens* is a distinct species.

Geographical Distribution.—In the western hemisphere, onchocerciasis has been found to originate only in rather sharply circumscribed areas in southern Mexico and Guatemala. It has been suggested that the disease may spread to the United States by infected immigrants coming over the border from Mexico, and that it may later become endemic in this country.

Johnstone and Larsen (1933) have called attention to this danger and have emphasized that physicians in the temperate zones and especially in the United States should become acquainted with onchocerciasis, since a species of the fly that transmits it (*Simulium*) is widespread in certain localities throughout the western states and the disease has shown a definite tendency toward northern migration.

Reports have been made of the occurrence of two cases of onchocerciasis in American residents of the southern United States. However, in neither of these has the diagnosis been accurately verified. The writer, after a microscopical study of pathological material sent him from one of these cases, was unable to confirm the diagnosis. In the other case, reported in a negro from Alabama, there was entire absence of any description of the parasite published. However, as the manifestations of the disease progress slowly, it may be encountered in the United States in individuals who have formerly traveled or lived abroad in the infected districts. Caucasians as well as Indians, those of mixed blood and Negroes readily contract it in such localities. Dampf (1942) points out that the new Trans-American highway passes very close to or goes through the infected districts in Mexico, which may increase the spread of the disease.

Carlos Estévez and Martinez Baez (personal communication, 1944) report that the disease is on the increase in both Guatemala and Mexico. General Hugh S. Cumming, Director of the Pan American Sanitary Bureau, has appointed an Inter-American Commission to carry on further investigations regarding the disease and its prevention in these countries.

Cases have been diagnosed in Europe in the past few years by Mühlens and Nylius in Hamburg (1932), Joyeux, Sédan, and Esménard (1936) in France and Marbaix and Appelmans in Belgium (1936). Also Adams (1937) in Liverpool reported a case of keratitis of both eyes in which there was a high eosinophilia and in sections of the cornea Onchocerca microfilariae were discovered.

In the western hemisphere, the condition, as far as is known, occurs endemically only in the mountainous regions of Guatemala, especially in the Departments of Chimaltenango, Solola and the northern part of the Department of Escuintla, on the southern or Pacific slopes, at altitudes between 2000 and 4500 feet, and also in similar and nearby regions in southern Mexico, especially in the states of Chiapas, Oaxaca and Guerrero. Dampf (1942) says that at the present time there are 20,000 cases in Chiapas and 11,000 in Oaxaca.

It does not occur at lower altitudes in Guatemala, and it is especially connected with the coffee production, the best coffee being produced in these regions and at these altitudes. It is in connection with the production of coffee that the inhabitants are especially brought into contact with the flies that transmit the disease, and these flies in Guatemala and Mexico do not breed below some 2000 feet. In Guatemala in the different coffee plantations from 40 to 60 per cent of the inhabitants were found infected.

Mira, in Guatemala (1936) found in a survey of 176 villages or towns in which 24,431 persons were examined that 30 per cent were infected. In Mexico, Hoffmann reported that in La Granja approximately 100 per cent of the natives were infected, and Mühlens and Hoffmann noted that in 1930–31 the infection rate rose rapidly in one district in Oaxaca from 10–20 per cent to 80–90 per cent. Torre found 15,000 infected in the state of Chiapas, and 5000 in the state of Oaxaca.

In Africa, the disease is common along the west coast from Sierra Leone and Liberia on the north to the Cameroons and the Congo on the south. In the Congo it extends eastwardly into Uganda and Kenya 1939 and Nyasaland 1939 and it has more recently been reported in the southern Sudan and in Kavirondo (1940).

The flies which transmit the disease in Africa breed in lower altitudes, below 1000 feet, and corresponding to this distribution of the fly we find the disease in Africa very common below 1500 feet—as in Liberia, Sierra Leone and parts of the Belgian Congo. The rate of infection varies considerably in the different districts in Africa. Thus Blacklock found in Sierra Leone that 45 per cent of 123 natives examined were infected. Brumpt, Rodhain, and Dubois, state that from 50 to 60 per cent of the natives in the different districts of the Congo are infected. Hissette reported that the rate of infection in the Katanga, in the village of Ilebo, was 73 per cent, and the writer and his colleagues found in Malele (Province of Lusambo) that almost every inhabitant of this village was infected.

Etiology.—The adult *Onchocerca* parasites are found in the nodules or tumors, either in dilated spaces or embedded in the connective tissue of the nodules. The male parasites, on account of their comparatively short length, often may be obtained unbroken and without great difficulty by dissection of the central portions of the tumors. However, the female parasites are so interlaced within tissue that they are very difficult to secure entire by dissection.

The adult parasites are white, opalescent nematodes with conspicuous transverse annular thickenings of the cuticle and reënforced externally by spiral thickenings (bagues). This cuticular ornamentation is an essential character for the recognition of the genus, *Onchocerca*. The body of the adults are filiform and tapering at both ends. The head is rounded and truncated with a diameter of 0.04 mm. The male measures from 18.8 to 32 mm. in length, by 0.13 to 0.21 mm. in greatest breadth. The alimentary canal is straight and ends in a subterminal anus. The tail terminates in a single spiral and is bulbous at the tip. The number of papillae is somewhat variable. Two pairs of preanal and two pairs of postanal frequently are demonstrable. Intermediate papillae also may be distinguished in some specimens. The two spicules are unequal, in some specimens measuring 0.082 and 172μ respectively and may be seen protruding from the cloaca.

The female is considerably longer, measuring 335 to 500 mm. in length, 0.27 to 0.4 mm. in greatest breadth. The vulva is situated 0.4 to 0.82 mm. from the anterior extremity, and the tail is curved. The uterus usually is filled with ova or embryos. The species is viviparous.

Since Sandground has found no constant morphological differences between *Onchocerca volvulus* and *O. caecutiens*, the latter name, therefore, should be regarded as a synonym though some suggest it may represent a biological race.

The microfilariae, which are found present in sections of the nodules and of the dermis or conjunctiva and other tissues of the eye, are actively motile. Great variations in size may occur. Two types are apparent; the smaller forms measure from 150 to 250μ, the larger forms from 285 to 360μ in length and from 6 to 8μ in width. They possess no sheath and are not found naturally in the blood. When, as might rarely happen, one has been seen in a preparation of the blood, it probably has escaped from a lymphatic vessel or space punctured in obtaining the specimen. Gopsill (1939) in prolonged careful examinations of the blood in cases of the disease in Nyasaland never found the microfilaria in the blood. However if a thin section of the epidermis of the face or neck or of the conjunctiva of an infected individual is made, 1 or 2 up to 4 to 8 motile microfilariae usually are found, and occasionally as many as 50 are observed.

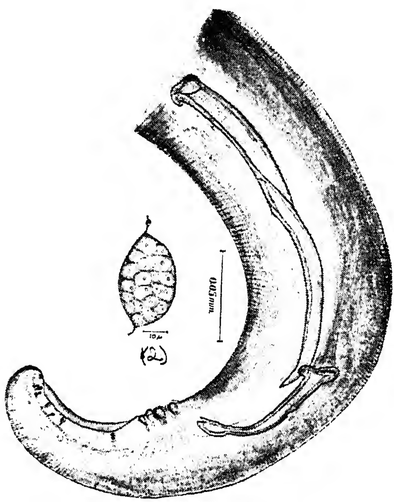

FIG. 308.—(1) *O. caecutiens*. Caudal extremity of male, lateral view. (2) *O. caecutiens*. Ovum taken from uterus, showing so-called polar filaments. Camera lucida drawings. Magnifications indicated by scales at side of figures. (After Sandground.)

In specimens hardened in absolute alcohol and stained with Giemsa's solution, the two forms of microfilariae may be sometimes distinguished. In the shorter but often slightly thicker forms there is a more compact arrangement of the nuclei, and they take the blue stain more readily than the larger forms. Both have a thick nuclei-free anterior end and a similar free posterior extremity. In the small forms Blacklock (1926) found in the African parasite the cephalic clear area measured from about 5 to 8μ and the caudal clear area from 10 to 16μ. The first break in the column of nuclei was situated at from 22 to 25 per cent of the length. In the large forms the cephalic clear area measures from about 7 to 11μ and the caudal from 13 to 18μ. The first break in the column of nuclei from the cephalic end was at from 21 to 25 per cent of the length.

Ochoterena (1930), by vital staining of the microfilariae of the Mexican parasite, found that starting from the head the non-nucleated portion occupied 5.1 per cent of the total length; the pre-nervous region 24.2; the nervous ring 25.7 from the head and occupied 1.6 per cent. The exterior pore was 34.5 per cent; the cells of Rodenwaldt 63 per cent; the anal pore 90 per cent, and the nuclear column ended at 94 per cent.

The presence of the microfilaria has also been reported in the lymphatic glands, especially the inguinal glands. However, the adult parasites have not usually been found in man outside of nodules or tumors. Whether the microfilariae are *generally* found in the deeper tissues and the viscera is still questioned.

Macfie and Corson performed autopsies upon 3 cases in the Gold Coast, in which microfilariae were found in the skin, but they were not present in the viscera. However, in these cases no nodules were found, and the adult *Onchocerca* parasites were not discovered in any part of the body, though they were looked for.

In 1931 the writer reported upon a patient 29 years of age, with a tumor of the head and loss of vision in both eyes, who died apparently from general peritonitis. Permission was obtained to perform only an incomplete autopsy. Adult *Onchocerca* were found in the tumor. Microfilariae were found in large numbers in the periphery of the tumor, in the skin, in the corium, and in the eyes, especially in the cornea. The examination of film preparations made from the liver and of the stained sections of this organ showed no microfilariae. Rodhain and Gavrilov 1935, reported upon the histological studies of tissues which had been sent them from a fatal case of leprosy occurring in Leopoldville, Belgian Congo. However, neither during life nor at autopsy was there any report of the discovery of nodules or *Onchocerca* in this case. Apparently no blood examination had been made and no tissue from the skin or eye was sent to Rodhain for examination. Rodhain found in the sections pieces of microfilariae in the mammary gland and liver; in small numbers in the spleen; and a few in the kidney. They were also found in the cubital nerve. In this connection it should be noted that Klotz in 1930 reported upon the occurrence of microfilariae of *Loa loa* in the spleen. In 1937 Rodhain reported upon the histological study of the tissues of two other cases which had been sent him. In the first of these three nodules were found at autopsy by Dr. Lesman in Kasai. Rodhain found in the sections from this case that microfilariae were present in the skin in small numbers, but not in the deeper tissues or viscera. In the second case, there were no clinical details except that it had been stated that the patient had onchocerciasis. In decapsulating the kidney which was sent to Rodhain, he found a dozen adult *Acanthocheilonema perstans*. Apparently no sections of adult *Onchocerca* were found in the histological study, but microfilariae were found in the sections of the skin, as well as in the viscera. In sections of the tissues, it is often difficult to make a diagnosis of the genus of the infecting parasite from small pieces of the microfilariae. Nettel (1938) performed two other autopsies on cases in Mexico. He examined all the organs for microfilariae but failed to find them, although he found them in the cutaneous nodules or cysts. Hence in order to ascertain to what extent and how frequently the microfilariae invade the deeper tissues, further studies are desirable with complete autopsies in which adult *Onchocerca* are found, and histological study of the tissues is made.

Pathology.—The adult parasites are clearly the inciting factor in the production of the nodules or tumors. In addition to the production of the tumors, pathological conditions may result in the skin and in the tissues of the eye, especially the conjunctiva, iris and cornea, sometimes in the choroid and retina. In these lesions, which are generally of a mild, inflammatory nature, microfilariae are often present, and not the adult parasite.

The nodules or tumors are enclosed in a fibrous capsule and contain, especially in the central portions, usually several adult filarial parasites and numerous microfilariae, though the number of adult parasites in the tumor is variable. In some cases the tumors are spherical, in others they are lentil-shaped. They are found embedded in the subcutaneous tissue, particularly in regions where the peripheral lymphatics converge. Sometimes they lie in shallow depressions on the surface of the skull, the periosteum either being adherent to, or fused with the interior surface of the cyst wall. In some cases the periosteum apparently has become absorbed.

The appearance of the tumors studied in Gautemala and in Africa are similar. The structure of the tumors varies to some extent according

to their age. Usually they are firm and grayish white at the periphery, but there are often soft areas in the more central portions, and these sometimes have a yellowish or orange color. In other instances the central portions are composed of grumous material with a milky appearance. It is in these soft areas or cavities that the adult parasites are particularly found together with enormous numbers of the microfilariae.

Histological examination of the nodules shows that immediately about the parasites there is often, but not always, evidence of an inflammatory reaction of a granulomatous character. This is probably caused by the presence of the parasite. A few polymorphonuclear leucocytes and endothelial phagocytes are scattered about with more numerous small round cells, occasional plasma cells and eosinophils. The tissue about the cut sections of the parasites sometimes consists chiefly of fibroblasts and numbers of endothelial cells lying within a more or less organized fibrinous exudate. Such tissue, however, is not richly vascularized in the characteristic manner of granulation tissue,

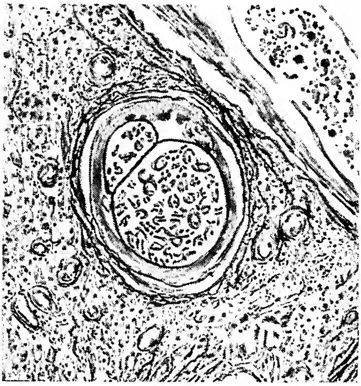

FIG. 309.

FIG. 310.

FIG. 309.—Drawing of fibromata with sections of Onchocerca volvulus cut transversely and longitudinally.

FIG. 310.—Drawing of section of fibroma caused by Onchocerca volvulus showing prevalence of collagen fibrils. (Camera lucida drawings (Zeiss objective DD, compensating ocular 6). Harvard-Liberian Expedition, 1930.)

and it has not the typical structure of a granuloma, such as is encountered for example in the granulomata of either yaws or of verruga peruviana. Outside of these areas of mild inflammatory reaction, the nodule is composed largely of fibrous connective tissue. In the older and larger tumors the fibroblasts may be few in number and the fibroglia fibrils not abundant, the nodules in such instances being composed particularly of collagen fibers forming wavy bundles. In none of the tumors is there marked evidence of mitosis; giant cells may be present in different portions, but usually they are not numerous. None of the tumors show any evidence of malignancy. However, Hoeppli, who studied one onchocercal tumor histologically, found numerous giant cells, and in several places the microscopical picture resembled that of a giant cell sarcoma. Martinez-Baez (1935), who has examined 61 pieces of tumors, which originated in Africa, Guatemala and Mexico, described especially granulomatous reaction about the parasites surrounded by more or less advanced fibrous and scleroid tissue. Giant cells were numerous in many of the Guatemala tumors. He found the structure of the nodules caused by *O. volvulus* and *O. caecutiens* essentially the same, though he describes minor histological differences, which he believes distinguish them.

The lesions found in the skin and tissues of the eye are in general, of a mild inflammatory nature with perivascular proliferation and infiltration of the tissues, with

lymphocytes, polymorphonuclear leucocytes and plasma cells, numerous microfilariae being present also. The eosinophils also usually are increased. The lesions in the skin and eyes are considered in detail under the subject of Complications.

Transmission.—The disease is transmitted by the bites of several species of small black flies of the genus *Simulium.* This fly is found breeding in the rather swiftly-flowing streams or brooks that abound in the infected districts, the larvae and pupae of the flies being attached particularly to the leaves and stems of plants, especially floating grasses growing or immersed in the running water, as well as to the surfaces of stones or logs. Blacklock, working in Sierra Leone, first showed that *Simulium damnosum* is capable of transmitting the infection in Africa and described the complete development of *Onchocerca volvulus* in this fly. Shattuck, Bequaert and the writer were able to find confirmatory evidence of this fact in Liberia a short time after Blacklock's publications in 1925. In 1931, Bequaert and the writer showed that in Gautemala three species of simulium are capable of transmitting the infection in Guatemala, as follows; *Simulium avidum* (syn. *S. metallicum*), *S. ochraceum* and *S. mooseri* (syn. *S. callidum*), while Hoffmann reported finding developmental forms of the parasite in *Simulium mooseri* in Mexico. Finally, Hissette, Bequaert, Sandground and the writer (1934) found that *Simulium neavei* may also transmit the infection in the Province of Lusambo. This has been confirmed for Kasirondo by McMahon (1940).

McMahon (1941) in Kenya found that practically all the flies were *S. neavei* and of 557 flies dissected 49 were infected.

The microfilariae, after being ingested by the fly, pass from the gut to the thoracic muscles. They first increase in length and then become very much broader, lose much of their motility and finally assume the "sausage form." After several moults have been accomplished the parasite assumes longer and more slender forms which possess marked activity and pass from the thoracic muscles particularly to the head and proboscis. We have repeatedly observed all stages of the development of the parasite in the fly from the time of the ingestion of the microfilariae from the skin of the infected individual up to the fully developed, infective, filarial forms in the thoracic muscles, head and proboscis.

In Guatemala about 5 per cent of the wild simulium flies captured in the endemic districts were found infected with the parasite. In one village in Lusambo, Belgian Congo, where the rate of human infection was very high, 33 per cent of the wild simulium flies were infected with the parasite.

Only the female fly bites and transmits the infection. The SIMULIIDAE are day-biting flies, beginning to bite about 6 a.m., and bite freely usually between 8 a.m. to 5 or 6 p.m. The face, neck, feet, ankles, wrists and arms of natives in the endemic regions usually are exposed, and the flies are frequently found biting in all these localities.

Mammalian Hosts.—In the study of the origin of the disease in Africa, examinations were made of the fauna of the different regions to ascertain if another mammalian host besides man could be found for the parasite *O. volvulus.* Species of *Onchocerca* were found in antelope and buffalo, *Bubalus caffer*, not giving rise to nodules and not identical morphologically with the former species. However, subsequently, in the eland, antelope, (*Taurotragus oryx pattersonianus*) subcutaneous nodules were found in which a species of *Onchocerca* was present, apparently identical morphologically with *O. volvulus.* Cattle in the region to the south and in West Africa also show nodules containing this same species of *Onchocerca* (Cameron, Le Roux, and the writer). It seems probable that in onchocerciasis a species of antelope may sometimes act as a reservoir of the parasite. It also seems possible that human infection may have been originally acquired from wild animals or cattle. In a pygmy village where Simulium were highly infected, the inhabitants also were badly infected with onchocerciasis. Pygmies,

as is well known, spend a large part of their life in hunting wild game. They do not till the soil or have any regular agricultural pursuits. Now that strains of the parasite have been thoroughly established in man in Africa, Guatemala and Mexico, they are transmitted by *Simulium* from man to man entirely independently of other animals.

Clinical Features. INCUBATION PERIOD.—The development of the nodules or tumors occurs slowly, but there is evidence of the occurrence of small nodules in children under one year of age. Robles reported the presence of a nodule in 2 children under 3 months of age. The writer has seen 6 cases in young children, 4 of whom were not over 10 months of age. The rate at which the nodule increases in size probably varies in different individuals and with the number of adult parasites within the tumor. Also, the tendency to keloid formation in some cases may be one factor.

AGE, SEX AND RACE.—The nodules, while not uncommon in children, are more common in adults. Men are somewhat more frequently infected than women. In Africa, infection in white men has been rather rare, only some 20 cases have been reported. However, in Guatemala, infection in Europeans is not very uncommon.

SUBCUTANEOUS NODULES.—The subcutaneous nodules or tumors vary in size from 2 to 3 millimeters up to some 5 or 6 centimeters in diameter. The larger tumors are usually of more than 3 or 4 years' duration. They are firm to the touch. Their number and location vary greatly in different individuals and in different parts of the world. In parts of Africa, as Sierra Leone, Liberia and in Guatemala, the number of tumors usually varies from 1 or 2 up to 5 or 6, though rarely even more nodules may be present. On the other hand, in the Province of Lusambo large numbers of people were found with from 25 to 50 small nodules, and some with 150 or more.

The great variation in the number of nodules or tumors in different localities, as for example in Guatemala and Lusambo, or even in the same locality, may be explained in part on the basis of the different number of times that the individual has been bitten with infected flies. In Guatemala, where the number of nodules per infected person is not usually over 1 to 3 or 4, we never found, in any district in which we worked, more than 5 per cent of the wild *Simulium* flies caught in the village infected with the parasite, but in Lusambo, Bequaert, Sandground and the writer found as high as 33.3 per cent of such flies infected. Although a single infected *Simulium* may contain sometimes as many as 10 infective larval forms of the parasite, in other instances only 1 or 2 of these infective forms are found in a fly. Hence it is probable that an individual with over 150 nodules has been bitten by many infected flies.

In Guatemala and Mexico, the tumors are commonly situated in the region of the head, especially on the scalp, comparatively few upon the trunk. However, in Sierra Leone, Liberia, and parts of the Belgian Congo, the tumors are usually found on the trunk, especially in the intercostal spaces, in the axillae, on the back, around the pelvis, and sometimes in the region of the joints; rarely on the head. On the other hand, in the Province of Lusambo, Central Africa, one may find numerous small nodules widely scattered over the head, shoulders and trunk.

A satisfactory explanation can not be given regarding the tendency to the location of the tumors upon different parts of the body in different geographical regions. It has been suggested that the point at which the fly bites may be an important factor in determining the location of the tumor, and Blacklock has given some evidence that this may be a factor. However, there is not yet convincing evidence of this. In Guatemala, where nodules occur so commonly on the head, the flies are found frequently biting upon the legs, and the tumors are not found in Guatemala about the lower extremities. Also, the scalp of the natives is generally covered with coarse bushy hair, and most of the natives wear hats in the day time, when the fly bites. The tumors

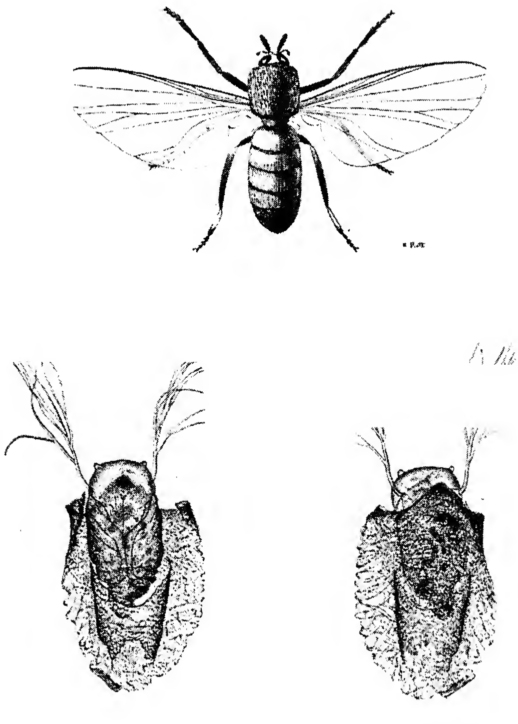

Fig. 311.—(Above) Simulium damnosum. (Below) Dorsal and ventral aspects of pupa and cocoon of Simulium. (Liberia. After Bequaert.)

often form on parts of the body where the lymphatics converge and where pressure for various reasons is likely to occur. It seems possible that the frequency of the nodules on the head in Guatemala may be influenced by the lymph vessels of the subcutaneous tissues of the head becoming constricted in some way by hats or head bands worn in the daytime, or by the head resting upon a hard pillow or some wooden object at night, as is customary there.

The tumors, when situated upon the trunk, usually cause little or no inconvenience, though sometimes they cause pain. They rarely suppurate and give rise to abscess, but in a few instances where death of the adult parasites has occurred, or secondary bacterial infection, abscess has resulted. When the tumors are located about the joints they are

more likely to cause disturbance by becoming inflamed and painful. When they are situated in the region of the scalp or about the shoulders, ocular complications are more likely to result eventually.

CASES WITHOUT NODULES.—While in the majority of the human cases of onchocerciasis, sooner or later a definite nodule forms about the adult *Onchocerca* as a result of the irritation which the parasite exerts in the surrounding tissues, there are instances of human infection in which there are microfilariae present in the skin in which no nodule or tumor can be recognized, and when there has been no history of a tumor. In horses, cattle, buffalo and antelope, adult parasites of species of *Onchocerca*

FIG. 312.—Slightly developed or second larval stage of *Onchocerca* in the thoracic muscles of *Simulium metallicum*, approximately 48 hours after feeding upon infected patient. (Harvard Onchocerciasis Report, 1934.)

(some identical in morphology with *O. volvulus*) may occur in the regions of tendons, especially the ligamentum nuchae, and not inclosed within definite nodules.

The writer, especially for these reasons suggested that the human species of *Onchocerca* may also sometimes occur in man in similar situations, or free in the subcutaneous tissue. However, although the adult *Onchocerca* has been known in man since 1893, it is only comparatively recent that a report has been published in which an entire adult parasite has been found in man outside of a nodule. Sharp, in 1927, identified as a portion of a female *Onchocerca* a fragment of a worm which a dresser had removed from an ulcerated condition of the foot, but Rodhain and Broden pointed out that this parasite might have been set free from a nodule by suppuration. However, van den Berghe (1936) has reported that in two autopsies upon individuals infected with *Onchocerca* and showing nodules, he found free adult parasites. In one case, a female parasite was found in the connective tissue in the region of the right trochanter and three fragments of a worm in fibers of the fascia lata of the right thigh. In the second case, an adult female parasite was found free in the dense connective tissue of the right trochanter. (See also p. 1370, Nettel.)

Blood.—The differential count of the leucocytes usually will reveal an eosinophilia. Montpellier and Lacroix have called attention to the high increase in the eosinophile cells in the blood in infection in Africa. In Guatemala the writer and Bennett have found eosinophile counts varying from 25 to 50 per cent, while Hoffmann (1930) in Mexico found counts varying between 20 and 75 per cent with an average of 37 per cent.

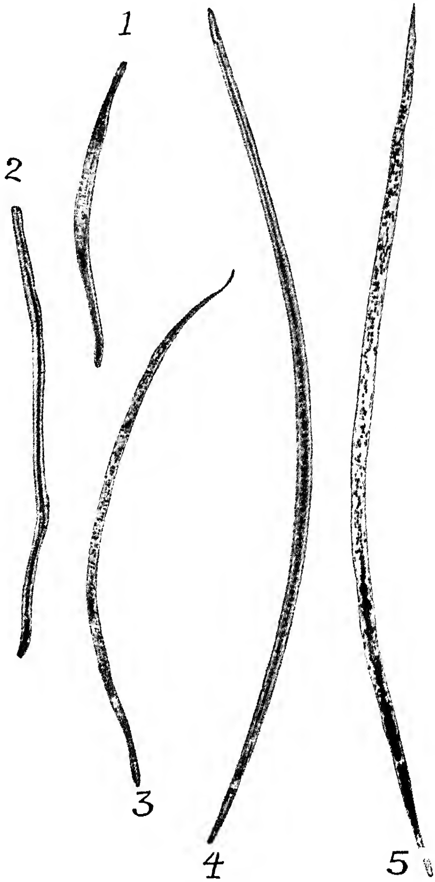

FIG. 313.—Third and fourth stage larval forms of *Onchocerca* from *Simulium;* forms 3 and 4 are approaching the type of the form infective for man; form 5 is the infective form for man of microfilariae (*Onchocerca caecutiens*) from the head of *Simulium.*

Complications.—In many individuals that apparently possess a special susceptibility to the products of metabolism and perhaps to the presence and movements of the parasites, inflammatory lesions occur in the eyes and in the skin. However, in many other individuals these secondary disturbances do not result. The origin of these secondary lesions is not entirely clear. It has been suggested that the inciting factor is (1) a circulating toxin that has been excreted by the adult parasites in the

nodules, or (2) the presence and movements, the products of metabolism, and death of the microfilariae in the skin and eyes.

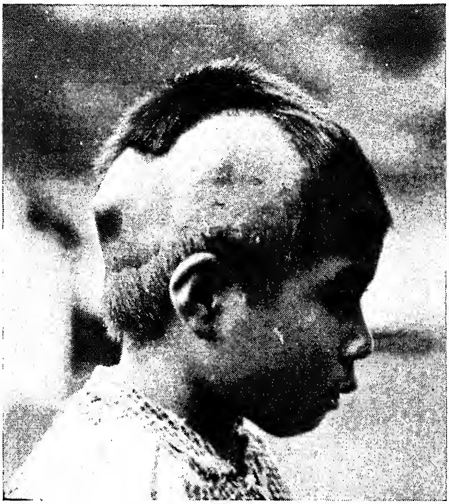

FIG. 314.—Onchocercal tumors of the scalp. Guatemala. (Harvard Onchocerciasis Report, 1934.)

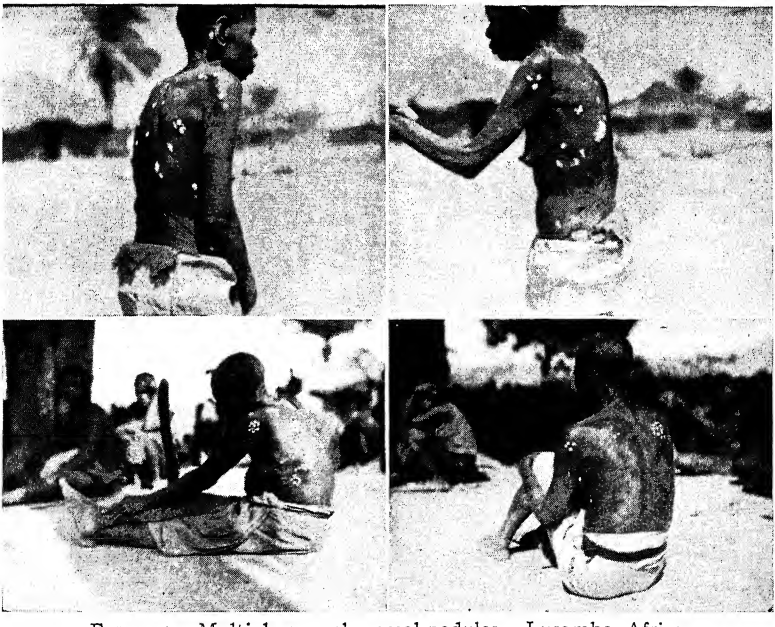

FIG. 315.—Multiple ononchocercal nodules. Lusambo, Africa.

Rodhain and Dubois (1931) suggested that the prurigo in connection with disturbances of the skin occurred as the result of an allergic reaction, a sensibility to filarial antigen, which varied in different individuals. D'Hooghe thinks that the microfilariae

play only a secondary role in the cutaneous lesions, and that they are due to allergic reactions, depending upon the antigen liberated by the macrofilariae in the sensitized human host especially at the time of birth of the microfilariae. Hissette believes the ocular disturbance due to the microfilariae themselves, and not to a toxin excreted by the adult parasites. Opinions are, therefore, divided as to what is the most important

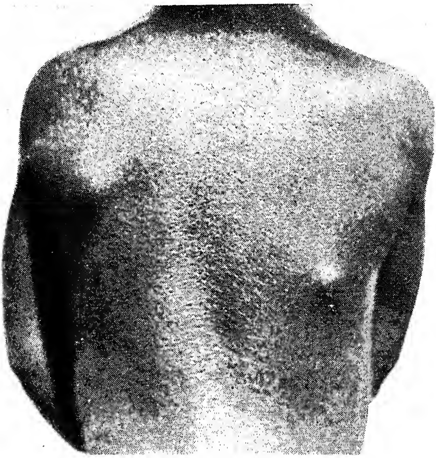

FIG. 316.—Onchocercal nodule with xerodermatic condition of the skin.

FIG. 317.—Section of skin illustrating many microfilariae in corium.

inciting factor in bringing about the inflammatory changes. Shafi believes that the skin reaction produced by onchocercal infestation varies with the severity of the infection. The writer thinks that while severity of the infection is one factor of importance, the susceptibility of the patient is apparently a very important additional factor. Rodhain and Dubois found in skin tests made with an antigen obtained from *O. volvulus*, *Loa loa* and *Ascaris*, that a much more lively reaction was obtained in patients who were

subject to prurigo. In one person with *O. volvulus* infection and no prurigo, there was no skin reaction. The role that the microfilariae play in the production of the inflammatory changes is not clear. It is well known that microfilariae of other species of

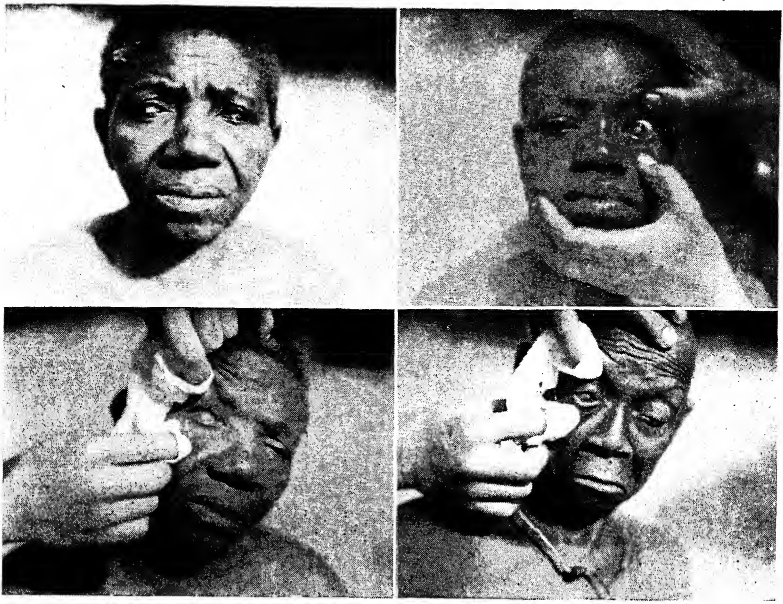

FIG. 318.—Ocular onchocerciasis. Cases with advanced keratitis. Africa.

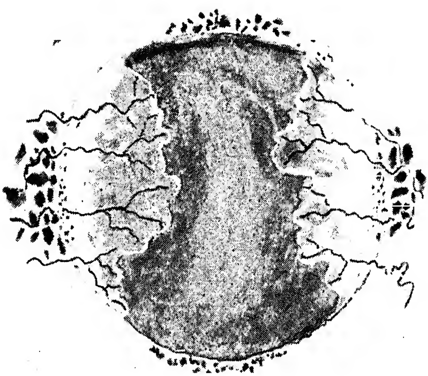

FIG. 319.—Onchocerciasis with lateral formation of pannus. (After Hissette.) In Harvard African Expedition Report.

Filaria within the blood vessels produce no lesions. However, the onchocercal microfilariae are not within the blood vessels.

In this connection, it is of interest to recall that Klotz, who studied in two cases the effect of *Microfilaria loa* in the spleen, found about groups of microfilariae, an inflam-

matory reaction and fibrosis, and numerous endothelial cells and eosinophils. He emphasizes that the temporary resting of the microfilariae within the visceral capillaries is unaccompanied by tissue reaction, while a more permanent abode of them as seen in the spleen is associated with inflammation and fibrosis. Rodhain (1937) in the study of the tissues from a case of onchocerciasis complicated with *Acanthocheilonema perstans* infection, found in the skin a cellular infiltration and some atrophy of the papillae, but did not find any lesions in the liver associated with the microfilariae encountered there, which were either *Microfilaria perstans* or *Microfilaria volvulus*. In onchocerciasis observations have merely shown that in the skin and conjunctiva and other portions of the eye in which the microfilariae are numerous, inflammatory reactions may occur, and

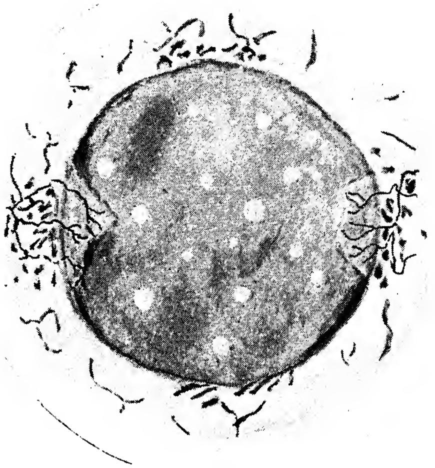

FIG. 320.—Ocular onchocerciasis, punctate keratitis, and early lateral pannus. (After Hissette.)

that it seems probable that their presence, products of metabolism, death and disintegration, are of importance in the production of the lesions in question.

Skin Lesions.—Since the investigations of O'Neil and Montpellier and Lacroix in 1920, it has been recognized that one form of "craw-craw" or "gale filarienne" is a dermal manifestation of onchocerciasis.

In old cases of the disease, pruriginous and xerodermatous conditions may be observed. The skin lesions sometimes consist of isolated or confluent pruriginous areas in which there is slight induration and sometimes slight changes in pigmentation. The inflammatory process is frequently increased by scratching. In such areas sections of the skin show a few or numerous microfilariae in the corium, with perivascular proliferation and infiltration of the corium, with lymphocytes, polymorphonuclear leucocytes, or plasma cells. The eosinophils in the skin are frequently numerous. In other cases, generally of long duration, a xerodermatous or sclerodermatous condition of the skin is present. In sections of such skin, microfilariae are frequently found, usually with more or less cellular infiltration of the corium, and in some areas the sebaceous or sweat glands are few or absent, and there are changes in the

thickness of the horny layer of the skin. However, in some cases with advanced lesions, no microfilariae at all are encountered in the corium.

It should be recalled that the microfilariae in the subcutaneous tissues are probably in constant motion. At one moment, a moist, minute section of the skin may reveal as many as 100 motile microfilariae. A short time afterwards or the following day a section of the skin made close to the same locality will reveal only several or no microfilariae whatever. Great changes in the number and in the presence or absence of microfilariae from certain areas of the skin at different times have been repeatedly demonstrated.

The advanced lesions of the skin have been studied particularly by Fülleborn, D'Hooghe, and Rodhain and Valcke. D'Hooghe (1934) observed 6 cases in Europeans, in 3 of which there was marked prurigo. He regarded the pruriginous lesions and the periodic engorgement of the tumors as due to an allergic response to an antigen which was probably produced at the time of periodic birth of the microfilariae.

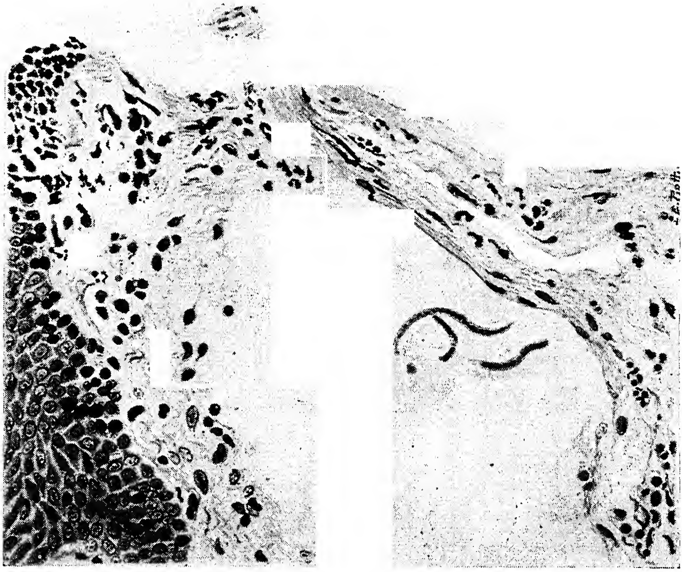

FIG. 321.—Microfilariae lying in oedematous area or lymph space in the pericorneal conjunctiva region of ciliary body. (Onchocerciasis Report, Harvard, 1930.)

Rodhain and Valcke (1935) have also examined 4 more cases in Europeans in which microfilariae were present in the fluid from the punctured nodules, though none were seen in the skin, although pruritis was marked in all of the cases. They believe that this evidence also supports the view that the embryos play only a secondary rôle in the sensitization of the skin, and that the absence of microfilariae in the skin in cases with chronic prurigo supports the theory that the prurigo may be considered as a manifestation of allergy depending upon infection with *Onchocerca volvulus*.

As Gibbons and Loewenthal (1933) suggested, it seems possible that the skin changes *sometimes* seen in onchocerciasis may be influenced or even due to long-standing attacks by *Simulium* whose bite can sometimes irritate for a period of a week. In individuals especially susceptible to the irritating effects of the bites of these flies, the toxin introduced by the bite is evidently sometimes a contributing factor in bringing about the inflammatory changes and lichenification sometimes observed.

Robles first pointed out that the parasite sometimes produced a definite type of erysipelas which was termed *erisepela de la costa*. The erysipelas usually occurred about

the face and eyes and there was often a rise of temperature. This condition was also noted by other Guatemalan physicians. It has been suggested that it is an allergic phenomenon, or that, perhaps by scratching, a bacterial infection of the skin with a streptococcus has been superimposed upon a lymphatic system in which circulatory disturbances had already occurred, which leads to the erysipelas.

Elephantiasis and hydrocele have also been reported by at least ten investigators as complications of onchocerciasis in Africa. Laigret reported a case in which there was a *volvulus* cyst upon the side of the chest from which numerous microfilariae of *O. volvulus* were obtained. There was also elephantiasis of the left foot and beginning on the right. However, upon centrifugation of the blood, microfilariae of *A. perstans* were also found. Chesterman (1935) in Yakusu has observed many cases of elephantiasis with elephantoid scrotum up to eight and ten pounds in weight, together with large and pendulous groin glands. D'Hooghe (1935) in the Congo also encountered elephantiasis and adenolymphocele in cases of onchocercal infection. In these regions infection with *Microfilaria bancrofti* and *Microfilaria perstans* are common. Van den Berghe (1937) also noted the presence of microfilariae resembling microfilariae of *Onchocerca* in genital elephantiasis. In Guatemala no case of hydrocele or elephantiasis has been reported as a complication of onchocerciasis. In the regions in which onchocerciasis occurs in Guatemala, other forms of filariasis are not encountered. We observed one case of elephantiasis of the leg in Guatemala outside the onchocercal endemic regions, but there was no evidence that it was of filarial origin. Obviously if the onchocercal parasites should block and cause lymphatic obstruction, and bacterial infection supervene, elephantiasis might well follow. In the great majority of the cases the onchocercal parasite evidently comes to rest in the more superficial tissues. The numerous authoritative reports from Africa show that elephantiasis sometimes occurs in that country *in association* with onchocercal infection, though it is not so common as it is in association with *Wuchereria bancrofti* infection. The fact that elephantiasis occurs in Africa as a complication of onchocerciasis, and not in Guatemala, clearly indicates that the elephantiasis is due to another factor besides the presence of the parasite. The importance of secondary bacterial infection in elephantiasis associated with *Wuchereria bancrofti* infection is now well recognized. Swelling of the lymphatic glands is not a complication of onchocerciasis that has been frequently noted, though microfilariae have been found in the inguinal glands on a number of occasions, a fact emphasized by Rodhain (1936).

Ocular Complications.—Robles (1916) first called attention to the ocular complications in cases of onchocerciasis in Guatemala. His observations were confirmed and extended shortly afterwards especially by Luna and Calderon. In Mexico the lesions of the eyes have been studied more recently by Ochoterena, Torroella and Silva, and in Africa by Hissette (1932), Bryant (1935), d'Hooghe (1935), and in Guatemala and Africa by the writer.

The ocular disturbances are believed to occur only late in the disease and usually after the infection or nodular lesions have persisted for some 5 or 6 years or more. They generally have an insidious onset. Photophobia in many cases is the symptom which first disturbs the patient. In other instances, the discomfort and irritation usually incident to conjunctivitis is first noticed, or epiphora may become troublesome. Amblyopia when present is usually a later manifestation. In the early stages, conjunctival hyperaemia, especially near the margin of the cornea, is common. Hissette has pointed out that the perikeratic redness in this condition which is of importance is that caused by the deeper lying ciliary vessels in the inflammatory reaction of the ciliary body, rather than that due to the injection of the superficial vessels. In some instances an

iritis beginning at the pupillary border is first noticed. After the iritis has developed, the pupil is usually contracted and small, and sometimes irregular. In some instances myosis results. Photophobia and epiphora are common at this stage of the infection, and impaired vision has already resulted.

Later the aspect of the iris itself may change, becoming thickened and altered in color, and covered with exudate. Hissette (1937) emphasizes that iridocyclitis, which develops slowly and is characterized by the contracted pupil, the dull clouded iris and the perikeratic redness, is one of the most characteristic and constant lesions of onchocerciasis. If it continues to progress for a long period, a permanent disturbance of the function of the iris is produced. By special illumination and magnifying lenses, in some instances he has observed a fine precipitate on Descemet's membrane, or a deposit of pigment on the anterior surface of the crystalline lens where there were adhesions of the iris. Most of the cases with such lesions had already reached the stage of blindness. In many cases, synechias occur, causing the pupil to assume an irregular shape. After repeated attacks, the iris in the region of the pupil may become adherent to the anterior surface of the capsule of the crystalline lens by a ring of synechias, causing seclusion, or later even occlusion of the pupil. In the late stages of the disease, atrophy of the iris may also occur, with disappearance of the pigmented border of the iris and thickening of the walls of the blood vessels, and sometimes alteration in the pigment cells.

In other cases, small areas of opacity in the cornea may first attract attention (punctate keratitis). These may increase in size and become confluent. Vascularization of the cornea frequently follows and in many cases pannus becomes well developed. In the earliest stages of the keratitis, the size of the opacities in the cornea are so small they can only be detected by the aid of a slit lamp and the corneal microscope. Later they may reach one millimeter in diameter. They may be located between the epithelium and Bowman's membrane in the body of the cornea. At this stage of the disease, the sensitiveness of the cornea is greatly lessened or is lost.

In some advanced cases, a deep or ciliary vascularization is present in the deeper layers of the cornea, giving rise to an interstitial keratitis. This lesion appears either when pannus is already established or at the time of its onset. In such cases, precipitates may sometimes be seen upon the endothelium which lines Descemet's membrane. Bryant (1935), in a study of "Sudan blindness" in the Anglo-Egyptian Sudan, which he believes due to infection with *Onchocerca volvulus*, found the opthalmoscopic appearance to be that of a diffused retinochoroiditis with optic atrophy, often with sclerosis of the retinal vessels and the deposition of masses of pigment on the retina. Advanced keratitis was also found in some cases. Hissette has more recently (1937) called attention to the importance of pigmented retinochoroiditis in onchocerciasis, and emphasizes that the process often results in dystrophy of the optic nerve and later in atrophy, and is the cause of blindness in many cases.

Histological Studies.—Histological studies show that in the bulbar conjunctiva, especially near the margin of the cornea, the lesions resemble somewhat those seen in sections of the skin. There is often more or less marked perivascular proliferation, and infiltration of the surrounding tissue with endothelial leucocytes, and small groups of lymphocytes, polymorphonuclear leucocytes, and plasma cells may be present. In one instance hyaline degeneration of the connective tissue fibers of the subconjunctival tissue was present (resulting in pinguecula), and the conjunctiva richly invaded with microfilariae. Small cysts of the conjunctivae were also observed in three cases, and dilated lymph spaces in several others, in all of which microfilariae were plentiful in the conjunctiva.

In advanced cases fibroblasts and fibroglia fibrils may be present. Similar lesions are found in the iris and cornea. In the cornea, especially near the periphery, vascularization has often occurred. The capillaries are in places dilated, and among the newly-formed capillaries there is infiltration with leucocytes, plasma cells, and occasional fibroblasts. The epithelium on the surface of the cornea is sometimes irregular, being thinned and destroyed, or in other instances is hyperplastic. Exudate containing lymphocytes and sometimes fibroblasts may also be present between Bowman's membrane and the substantia propria. In places the membrane may be destroyed. Less frequently these changes may be seen in the deeper layers of the cornea proper. In a few advanced cases separation of Descemet's membrane has occurred. The microfilariae are found in the conjunctiva, cornea, and iris, sometimes in association with groups of lymphocytes. However, they are often absent from these areas but present in adjacent fields of the microscope. When alive they are apparently continually moving. In places in the cornea the writer found them, when from their appearance and uniform staining reactions they were probably dead. In the anterior portions of the cornea they are found particularly in spaces in the tissue, which they apparently create by their movements, and in the lymph and newly-formed perivascular tissue spaces. Hissette has observed in addition general uveitis with degenerative lens changes and discrete retrobular optic neuritis.

Prevalence of Ocular Complications.—The prevalence of the ocular complications varies considerably in the different regions. In Mexico (in Chiapas) Larumbe (1926) reported that of 4,000 cases of onchocerciasis about 800 developed keratitis, iritis, and choroiditis, and 100 were totally blind. Mühlens (1932) writes that at LaGranja, Chiapas, about 10 to 20 per cent had ocular disturbances. In Guatemala (1931 and 1932) among our onchocerciasis cases, disturbances of the eyes were encountered in only about 5 per cent. However, only the robust and well would find employment in the privately owned coffee plantations, and the percentage with ocular lesions might be higher in Indian villages away from these plantations. In fact, Mira, Diaz, and Estévez (1935) found that in the examination of 742 cases about 6 coffee plantations in Guatemala, 34.8 per cent complained of photophobia, and 15 per cent suffered with amblyopia.

Hissette, in the northwest Congo, found disturbances of the eye very prevalent. In the village of Ilebo, of 150 persons, 68 had disturbances of the eyes due to onchocercal infection; 15, or 10 per cent, were blind; 42 of the 68 with disturbances of the eye had nodules upon the head.

Bryant (1935), who has made a study of "Sudan blindness" in the Anglo-Egyptian Sudan, believes a large amount of it is due to *Onchocerca volvulus* infection. In a number of cases of "Sudan blindness," 58 per cent gave visible evidence of *O. volvulus* infection, or 49 per cent more than the average of the adult population.

Cruickshank (1934) has also emphasized that 4.5 per cent of the Anglo-Egyptian Sudan population suffer from endemic blindness, much of which is due to onchocerciasis.

Although ocular disturbances had been recognized in Guatemala since 1916, prior to 1931 the association of ocular disturbances definitely due to the disease in Africa had not been demonstrated. However, in a very high percentage of the cases observed, the tumors had been encountered upon the trunk or extremities and not situated upon the head.

Thus, D'Hooghe (1935) in the examination of 3448 natives, found that 2.1 per cent presented ocular complications, and that 0.4 to 0.5 per cent had become blind. However, in the very great majority of the cases nodules were situated upon the trunk, the number of fibromata upon the scalp being only 5.7 per cent.

Blacklock, in Sierra Leone, where nodules on the head were found only in 8 cases, observed no ocular lesions.

Relationship to Tumors.—Experience in Africa and Guatemala seems to indicate that those individuals in which the nodules or tumors are located upon the head or shoulders are more likely to suffer with disturbances of the eyes; and that in cases in which the tumor is located at considerable distance from the head, ocular lesions are more often absent. It has been conclusively demonstrated that the microfilariae are generally

found in greatest numbers in the skin in the vicinity of the tumors, and that at considerable distance from the tumors very few or no microfilariae may be encountered. In Guatemala the microfilariae were found in the skin most abundant in that of the face; usually very few or none in that over the ankles or feet.

In cases with tumors upon the head, neck, or shoulders, microfilariae do not have so great a distance to reach the eyes as they would in cases with tumors upon the trunk or joints, and they are frequently much more numerous in the ocular conjunctivae in cases with nodules about the shoulders and head than in cases with nodules elsewhere in the body. It would appear that the continual penetration of the dense connective tissue of the cornea by large numbers of microfilariae, and the death of many of them there and in the other tissues of the eye, may exert a pathological effect as well as any toxin which is produced by the parasites.

Obviously it would be wrong to conclude, because microfilariae are merely present in small number in the bulbar conjunctiva, that the disturbances of the eye are necessarily due to the filarial infection. It should be emphasized that in many cases of onchocerciasis the microfilariae in the skin may not produce any disturbance of moment. So also in the eye, the mere presence of a small number of microfilariae in the bulbar conjunctiva may not give rise to any lesions of the eye that are demonstrable. In many tropical countries disturbances of the eyes are common for various reasons, the individuals being predisposed to such affections through their low degree of intelligence, their poor knowledge of hygienic conditions, and their general mode of life. In tropical countries, heat, wind, dust, and smoke within the house or hut are all important in bringing about ocular disturbances. Avitaminosis, xerophthalmia, especially when associated with bacterial infection, trypanosomiasis and arsenical poisoning may also be responsible for much blindness in regions where onchocerciasis prevails.

Movements of Parasites in the Eyes.—A symptom sometimes complained of is that relating to entoptic vision of the microfilariae crossing the visual field. Muhlens and Hissette have reported that some of their patients have complained of seeing movements within the eye. In one of Hissette's patients, the movements described suggested somewhat those of mosquito larvae in water. To another patient, the forms seemed to be black in color, and to a third, as worms of fire. He suggests these symptoms were probably due to a localization of the microfilariae in the neighborhood of the retina or choroid near to the macula zone. Silva, with Gullstrand's ophthalmoscope, has reported that he has been able to see, in the vitreous humor, shadows of the moving microfilariae. Hissette has observed dead larvae with flakes of fibrin and pigment in the anterior chamber while Boase (1935) in Uganda saw the microfilariae moving across the aqueous humor in a blind school teacher.

Reid and Adams (1938) have also observed on two occasions with the slit lamp microfilariae in small numbers. The microfilariae removed themselves with remarkable rapidity from the bright light applied by the apparatus. They could only be observed for a few seconds before leaving the range of vision.

Quevedo (1941) believes the ocular troubles are caused by the microfilaria in the tissues and are not due to a toxin produced by the adult parasite. He has never failed to find microfilariae in any eye lesion caused by onchocerca. Later the microfilariae can be seen free in the anterior chamber. He has observed all the ocular changes which have been previously recognized.

Diagnosis.—The onchocercal tumors sometimes may be confused with dermoid cysts, lipomata, non-parasitic fibromata and especially with juxta-articular nodules. Onchocercal tumors simulate very well juxta-articular nodules and frequently affect the same regions, also, it is frequently impossible to distinguish clinically one from the other without microscopical examination.

The diagnosis of onchocerciasis may be made by puncture and aspiration of fluid from the nodular tumors and the discovery of the microfilariae in such fluid. Often several hundred parasites may be found in a single drop of the aspirated fluid. (See Fig. 322.) On the other hand, no microfilariae may be obtained, even though the nodule is onchocercal in nature. Sometimes only adult male parasites, or only female parasites or dead parasites are present in the tumor. If the microfilariae are not present

in such fluid, frequently they may be found in small sections of the skin removed by a safety razor blade. In fact, in a given series the examination of the section of the skin may give a higher percentage of positive findings than the examination of puncture fluid from the nodules. Most favorable results usually are obtained with skin removed from somewhere near the tumor. If the tumor is on the scalp, the cheek is a favorable place. The portion of skin should be transferred to a glass slide and a few drops of normal saline solution added, and a coverslip placed over it. No teasing of the skin is necessary. It is preferable that the sections of the skin should be sufficiently thin so that practically no blood is drawn in making the section.

In instances, in which no nodules are found, detection of the microfilariae in sections of the skin or of the conjunctivae is the only satisfactory means we possess for the diagnosis of onchocercal infection. However, if no microfilariae are found in the skin, it does not exclude the diagnosis of onchocerciasis, since they are sometimes absent in the skin, when true onchocercal nodules are present. In the great majority of cases, whether ocular lesions are present or absent, the microfilariae may be detected in thin section of the bulbar conjunctiva obtained with curved eye scissors. Diagnosis may sometimes be accomplished in an endemic center by the microscopical examination of the contents of the gut of a simulium fly immediately after it has fed upon an infected patient. Microfilariae sometimes may be encountered in the fly, often in considerable numbers, even when the direct examination of a section of the skin has been negative. The fly in feeding apparently causes a concentration of the microfilariae at the point of the bite.

In cases with no demonstrable nodules, sometimes the presence of eosinophilia 30 per cent or more may suggest the diagnosis, as was the case in a patient with ocular disturbances at the Liverpool School of Tropical Medicine in 1938. However, eosinophilia may of course occur in other forms of filarial infection (see p. 1378).

Nettel (1941) reports that in cases with ocular disturbances periauricular nodules are easily over looked; that nodules may occur in muscles and attached to fascial planes or other deep nodules may remain undetected. Of 40 cases with blindness periauricular nodules were present in all, and they are apt to produce oedema of the face and ear.

Immune Reactions.—Attempts to demonstrate any immune reactions in onchocerciasis have not been very successful. The writer and Bennet tried to ascertain if hypersensitive reactions could be obtained with an aqueous or alcoholic antigen prepared from the adult parasites or from tumors containing the adult parasites and enormous numbers of ova and microfilariae. Such antigens were employed in performing both an intradermal test as well as the precipitin reaction with the serum of cases of onchocerciasis in Guatemala. Both these reactions were found to be of practically no value in diagnosis. While in the majority of instances of onchocercal infection an intradermal reaction was obtained, a similar reaction was also frequently obtained in control cases with no onchocercal infection, and some onchocercal cases gave a negative reaction. The precipitin reaction was positive in a few, but negative in many of the cases.

Rodhain and Dubois have performed the intradermal test in 3 cases of onchocerciasis in Africa, using an antigen prepared from *Onchocerca volvulus* and *Loa loa* or *Dirofilaria immitis*. They state that the reaction is evidently a group one. Although positive reactions were obtained in the three onchocercal cases, they did not show the uniformity obtained by them in *Loa loa* or *Dipetalonema perstans* infection.

Fülleborn (1931) also prepared an antigen by drying a nodule excised from a case of onchocerciasis. The inoculation of this antigen in two cases with onchocerca nodules

gave typical wheals, but not only with them, but also with onchocerca-free controls sensitive to *Ascaris* and *Strongyloides* antigens.

Fairley (1931) using a *Dirofilaria* antigen states the skin test and complement fixation one were both partially positive in one case of onchocerciasis after removal of the nodule. Also, Rodhain and Van den Branden in onchocerciasis cases obtained no favorable results with the complement fixation test, using a *O. vulvulus* extract for antigen, while Montpellier and Beraud with such an antigen obtained 50 per cent of positive reactions in cases evidently not infected with onchocerca.

Also, Gutierrez in Mexico prepared an antigen made of portions of onchocerca parasites extracted from nodules and performed the complement fixation test. Positive reactions were obtained in all cases suffering from onchocerciasis, and also from syphilis and "mal del pinto" cases. He concludes that until this source of error has been eliminated, the reaction can have no diagnostic value in onchocerciasis.

Hoffmann and Vargas state that by using an antigen of Gutierrez they obtained a more marked skin reaction in controls in white people not infected with onchocerca than they did with infected natives. However, Van Hoof (1934), who has employed the method of complement fixation of Calmette and Massol, as modified by Mathis and Labougle, with an alcoholic extract of onchocerca, believes that the test is a definitely specific one. D'Hooghe (1935), who has also employed the intradermal reaction for diagnosis, concludes that in a region where several species of filaria are endemic, or where the inhabitants are almost always carriers of intestinal parasites, the intradermal reaction loses all value for diagnosis of onchocercal infection.

Wright & Murdock (personal communication, 1944) in performing skin tests with an antigen prepared from *Dirofilaria immitis* which had been dried and employed in a dilution of 1:4,000 found the reaction was not specific for the diagnosis of onchocerciasis since a positive reaction might be obtained in individuals harboring intestinal parasites and not onchocerca.

Differential Diagnosis. OTHER HELMINTHS AND OCULAR DISTURBANCES.—So far no one has removed or demonstrated definitely an adult *Onchocerca* parasite in the tissues of the eye, though the presence of the adult worm in the eye has been suggested. However, several parasitic nematodes besides *Onchocerca* have been encountered in connection with ocular disturbances. Of these the most common is *Loa loa*, and from the frequency that this adult worm has been observed in the region of the eye, it would appear that it has a special predilection for that region.

Wright (1934) and Fernando (1935) have reported upon the presence and removal from the anterior chamber of the eye of an adult *Filaria* presumed to be *Wuchereria bancrofti*. Alicata and Morrison (1936) noted the presence of an adult *Dirofilaria immitis* in the aqueous humor of the eye of a dog. The symptoms observed in connection with the presence of this parasite were conjunctivitis, increased lacrymal discharge, and slight opacity of the cornea, as evidenced by the occasional desire of the dog to rub its eye. For the relief of symptoms the nematode was removed, and was identified by M. C. Hall, of the Bureau of Animal Industry, Washington, D. C. S. Sundar Rao (1933) has also reported cases of ocular disturbance with visible filariae beneath the bulbar conjunctiva, in which, however, the infecting parasite was not identified.

Noronha (1932) has reported from India frontonasal tumors, in a child, which were first diagnosed as dermoid cysts, showing inflammation and displacing the eyeball upwards. Dissection of one was followed by the child's death, section of the tumor showed a coiled *Filaria* containing embryonic forms. It was first reported that the lesions resembled those of *Onchocerca caecutiens*. Further study showed that the parasite was not *O. caecutiens* but *Dracunculus medinensis*. Owen and Hennessey (1932) in Uganda have studied series of cases in which there is oedema of the eyelids often accompanied by itching, known as "bung-eye," and one characterized by proptosis, designated as "bulge-eye." In both these conditions where were small yellowish nodules about 2 mm. in diameter situated in the deeper layers of the conjunctiva. Ten of the nodules were excised and sectioned. All of these showed a definite histologic picture. There was a mass of inflammatory tissue richly supplied with blood vessels.

In three cases the nodules contained worms, the fragments of the parasites occupying clearly-defined spaces within the areas of necrosis. The whole series of cases showed a high average eosinophilia. Embryos or ova were not found in the tissues. The possibility of such a worm belonging to the genus *Thelazia* was suggested by Leiper. Four cases of human infestation by *Thelazia callipaeda* have been reported from China. In two of these (Stuckey, 1917, and Trimble, 1917), the worms were found in the conjunctival sac. However, the latter patient suffered severe symptoms with ectropion and excessive lacrimation. In the third case (Howard, 1927) they occurred in the epithelial crypts of a wart-like papilloma of the lower eyelid which had been present for many years. In this case the affection had probably resulted from handling a parasitized dog some months prior to the removal of the papilloma. Leiper (1917)

FIG. 322.—Photomicrograph of larval forms of Onchocerca volvulus. Moist film preparation made from cut section of tumor. (Harvard Guatemala Expedition, 1930.)

and more recently Faust (1927) have demonstrated that the human and dog parasites in China belong to the same species, *Thelazia callipaeda*. A fifth case has been reported by Kofoid and Williams (1935) from California (the first in the United States). The patient had mild conjunctivitis, and 3 worms, 10 to 13 mm. in length, were removed from the eye. Kofoid has named this new species "*Thelazia californiensis*."

The clinical appearance in the cases of "bung-eye" and "bulge-eye" evidently differs greatly from that observed in the cases of human *Thelazia* infection observed in China.

Owen and Hennessey state that the question of the zöological status of the parasite which they found must rest in abeyance until further material has been obtained. It would appear unlikely that the parasite concerned is a species of *Onchocerca*.

Africa and Garcia (1936) have reported a case with itching and redness of the conjunctiva, with lacrimation, photophobia, and dimness of vision in the right eye. A diagnosis of chronic catarrhal conjunctivitis and keratitis was later made, and the removal of a small nodule in the lower palpebral conjunctiva was found to contain sections of a parasite, diagnosed as a species of *Cheilospirura*. The nematodes of the

genus *Cheilospirura* have hitherto only been reported as parasites between the tunics of the gizzard of birds in different parts of the world.

Babudieri (1937) has reported a case of human filariasis due to *Filaria conjunctivae* Addario 1885, with a nodule on the left cheek. He also describes in detail the parasite which was removed, and considers the 7 other cases of human infection that had previously occurred, in which cystic tumors of the eyelid, eyeball, and skin of the nose, and other localities had been reported.

Desportes (1940) has found an immature adult of "*Filaria conjunctivae*" and classifies it in the genus *Dirofilaria*. He also notes that the species has been found occasionally in cyst-like tumors of the eye, nose, arms and mesentery in Europe and in India. The female parasites are 15–20 cm. long and 0.5 mm. broad. The parasite is reported as causing a burning or itching sensation and localized oedema. One male *Dirofilaria repens* has been reported from a nodule in the eyelid of a woman in Russia.

Recent Reports of Diagnosis with the Ophthalmoscope and Corneal Microscope

Estrado Torres has found that microfilariae in the vitreous are most easily seen with the electric direct-image ophthalmoscope using a +20 to +40 diopter lens. Microfilariae seen with the ophthalmoscope by transmitted light resemble fine black filaments on a reddish background. They reminded him of the appearance of mosquito larvae in water. The microfilariae seen in the anterior chamber with the corneal microscope with direct light are white very fine active filaments with golden reflections. Torres points out the simplicity of the use of the electric ophthalmoscope in diagnosis of the affection and that general practitioners and nurses can detect microfilariae with it. He examined 11 cases of onchocerciasis and found the microfilariae in all by ophthalmoscopic examination of the vitreous.

Semadeni (1943) has reported upon the histology of the eyes of a Swiss geologist affected with onchocerciasis which he contracted either in the Sudan or in Algeria. The condition was diagnosed with a slit-lamp corneal microscope which revealed about 300 living microfilariae, especially in the anterior layers of the corneal parenchyma. The eyes showed reddening around the cornea which were slightly clouded by many inflammatory foci with slight panus formation in places on the corneal margin. There was an eosinophilia of 25%. The patient was given emetine and fouadin. However, he died as the result of a mountaineering accident. At the autopsy adult onchocerca were not found but sections of the eye confirmed the presence of microfilariae in it. They were practically everywhere where there were lymphatics; they were found in the corneal parenchyma where there was inflammatory reaction but no cellular infiltration around the microfilariae. They were also present in the subconjunctival tissue, in the iris and especially in the ciliary body. None were present in the choroid, vitreous humour, retina, lens or optic nerve. The slit-lamp microscope made possible the diagnosis during life.

Graham Scott (1944) has described an ocular syndrome in which, 1. oedema of the upper lid, 2. proptosis, 3. ciliary flush, and 4. oedema of the optic nerve occurred as unilateral phenomena in 2 patients with oncho-

cerciasis. He points out that this syndrome is not a familiar one in general ophthalmic practice and he suggests that a lymphatic block directly due to microfilariae or indirectly due to filarial toxemia, as in calabar swellings, is an explanation of the four symptoms. Microfilariae were demonstrated in both cases, in the eye or in the skin. In only one case were onchocerca nodules found.

Prognosis.—There is general agreement in the recent observations of Larumbe, Hoffmann, Mühlens and Hissette with reference to the ocular lesions only occurring as late disturbances and only usually after the infection or nodular lesions have persisted for some 5 or 6 years or more.

The idea previously expressed by some early observers that the removal of the onchocercal cysts resulted in the disappearance of ocular disturbances and a return to normal vision has been shown by many recent observations to be incorrect, especially through the observations of Hoffmann, Mühlens, Torroella, Silva, Hissette and the writer. The removal of the nodules, however, with the adult forms, if there are no other concealed adult parasites remaining, reduces the number of microfilariae circulating in the tissues of the eye and may arrest the ocular lesions, but if anatomical changes have already occurred, obviously removal of the nodule may have no perceptible favorable influence. Larumbe called attention to the fact that the amelioration of the ocular symptoms frequently occurred but sometimes for only 2 or 3 days following the operation, and after this period the ocular symptoms again became aggravated. Hissette has observed that this temporary improvement in many cases does occur, and he suggests that the temporary improvement in the symptoms may be an allergic response due to the onchocercal antigen set free in large amount by the traumatism which results from the operation.

A number of the early reports, in which the restoration of eyesight or an improvement of vision was believed to have occurred immediately following the removal of the tumor, are perhaps not so difficult to understand, when one considers the low degree of intelligence of many of the Indians among which the disease prevails and their superstitious and impressionable nature. Especially if the idea were suggested to them that their vision had been improved by the operation, they would generally be inclined to agree with such a suggestion. In Guatemala among many of the Indians in the infected districts there is a feeling that removal of the tumors does improve the ocular conditions. Especially does there exist the belief that the tumor after a time is likely to lead to ocular disturbances and to blindness. This is one of the reasons why the natives are willing and often eager to have the nodules removed, and through this circumstance the eradication and control of the disease is made more practicable in Guatemala.

Whether a toxin secreted by either the adult parasites or the microfilariae is responsible, or to what extent such toxins are responsible, for the ocular lesions, has not yet been conclusively demonstrated. The ocular lesions probably are influenced by the presence and movements of large numbers of microfilariae in the tissues, and the perivascular infiltration may perhaps result in a somewhat similar manner as occurs from the action of the trypanosome in the tissues of the central nervous system in sleeping sickness.

It seems probable that the circulatory disturbances in the tissues of the eye may predispose to secondary bacterial infections, and when occurring in the bulbar conjunctiva, predispose among other pathological conditions to pinguecula and to pterygium.

With the removal of the adult parasites in the tumors dermatological disturbances also appear to be at least sometimes ameliorated or perhaps prevented.

In patients with large numbers of nodules (over one hundred, for example), the prognosis is unfavorable both because such patients are evidently frequently exposed to reinfection and because it is impracticable to remove all the nodules, or to destroy by injection the parasites in all of them, as the patient will not submit to the repeated suffering from such a prolonged procedure.

Treatment.—The tumors or nodules should be removed in all instances, since individuals with such tumors, (unless the parasites within them are dead) constitute foci of infection if they reside in a district where the intermediate insect host is present. Their removal may also prevent dermal or ocular complications.

Although when they are situated upon the trunk the tumors may cause little inconvenience to the patient by their presence, when located about joints they are more likely to become inflamed and painful. When the tumors are situated about the head and shoulders, it is especially advisable to remove them in order to avoid or diminish the possibility of ocular disturbances. Even if in certain instances the adult parasites may be unenclosed in nodules and reproduce microfilariae in this free condition, removal of *visible* nodules should at least reduce the *severity* of the infection with microfilariae. The operations are simple and easily performed under local novocaine anaesthesia. From 40 to 50 cases may be operated upon in one day.

However, when the tumors are completely removed, the microfilariae do not always disappear following the operation, but may persist for a considerable time thereafter. Their persistence may be due in some instances to the existence of adult parasites unencapsulated or lying in concealed nodules. An attempt may be made to rid the patient of the microfilariae which may persist after the removal of the tumors (or which are present in individuals in which nodules cannot be found), by the use of filaricidal substances. The writer (1931) has shown that several drugs may be employed which effectively destroy the microfilariae *in vitro*. Among these are tartar emetic, fuadin, and plasmochin. Tartar emetic has exhibited the most filaricidal effect. Successful results have been reported by Wright and Underwood, and Khaw and Chen (1935 and 1936) in the treatment and cure of *Dirofilaria immitis* infection in dogs by injections of fouadin. Johnstone (1936) has also found that fouadin will destroy the microfilariae in dogs but not the adults even when the drugs used caused later the death of the dog. Brown and Sheldon have treated five dogs successfully with fuadin and sulfanilamide. In two of the five, living worms were found at autopsy but there were no larvae in the females. Tartar emetic, while more effective, is more poisonous than fouadin. While both of the drugs are certainly inimical to the existence of microfilariae, it is still doubtful whether the microfilariae in the body can all be destroyed by doses of these drugs which are not toxic for the patient. Harris (1941) found that after removal of nodules, treatment with intravenous antimony sodium tartrate was followed by disappearance of *microfilariae* from the skin and by a fall in the proportion of eosinophils.

Adams (1938) has reported a case in London with ocular lesions and microfilariae in the conjunctiva but with no demonstrable cutaneous lesions. In this case it was thought that a course of neostibosan arrested the progress of the eye trouble, though some microfilariae were subsequently found.

Lane (1938) does not believe that antimony compounds destroy the larvae, but thinks that they may sometimes sterilize the adult parasite and poison the ova, rendering it temporarily sterile. Murgatroyd (1938) believes the ocular symptoms are due to the microfilariae, since the surgical removal of the adults fails to effect a cure in many cases. He suggests that attempts at desensitization by graduated doses of filaria antigen may be a useful supplement to the other treatment.

Eradication.—In districts in which the disease is sharply circumscribed, as in parts of Guatemala, the eradication of the human foci of infection

is most important. However, protection from the bites of *Simulium* and destruction of these flies are most desirable in all countries where the disease prevails. In Guatemala the eradication of the *Simulium* concerned in transmission in the endemic areas is very difficult, for its breeding places are so widely distributed in practically every flowing stream of water in the neighborhood, and such streams constitute the only water supply of the districts. Eradication of the flies through attempting to destroy the larvae and pupae in the streams by changing the vegetation along the banks, by cutting and raking weeds on which the larvae or pupae are fixed, and by the removal of logs and stones or the scrubbing of them with stiff brushes, have all been suggested, but these are not very practicable preventive measures. Oiling of streams, particularly with phinotas oil, O'Kane has found, especially in New Hampshire, to offer a certain measure of value for control of *Simulium*. In streams or waterways in which fish of value are not present, the larvae may be rapidly killed, and the problem of concentration of the oil in the water does not offer much difficulty. Such measures would not be of practical value in Guatemala.

However, Dampf (1942) thinks creolin by the dripping method in small streams in Mexico is of value against *S. ochraceum* though only practicable in the dry season.

Opinions differ somewhat as to what have been the most efficient and practical measures for the eradication of the disease in Central America, of those which have been prosecuted against it during the extensive campaigns waged in Mexico and Guatemala in the past few years. Rosas (1937), Chief of the Federal Sanitary Brigade in Mexico emphasizes this fact.

Lorenzana, Chief of the Sanitary Brigade in charge of the control of onchocerciasis in the State of Chiapas, Mexico, from 1931–1933, emphasized the importance of the measures directed against the larvae of Simuliidae, and believes they constitute the only efficient method for the control of the disease in Chiapas. However, great difficulty was met with in carrying out successful anti-larval measures in that country, or in reducing the disease materially by them.

Observations made in Guatemala during recent years continue to show that the infected individual constitutes an important focus of infection and surgical removal of the tumors containing the adult parasites has been in vogue for several years in that country as a public health procedure of importance for the eradication of onchocerciasis. The writer believes that the *surgical* removal of the tumors, and complete and speedy removal of the parasites within them, is the procedure of choice. However, where surgical removal of a large number of tumors in large groups of patients is not practicable, and the patient objects to this procedure, or the number of tumors in the individual is large, the injection of the tumors with different drugs for the destruction of the adult parasites has been recommended.

In Guatemala where a systematic attempt has been made in sharply-circumscribed areas to eradicate it, the rate of infection has been materially lowered. In one plantation, Moca, where the campaign against the disease was rigidly pursued during 1931, upon re-examination of the inhabitants in 1932 the rate of human infection was found to be greatly reduced, as was also the rate of fly infection. However, the latter may have been somewhat influenced by the climatic factors in that area in 1932. During the next 4 years, when the campaign against the disease was relaxed, the rate of infection rose again. In 1935, an active campaign was again undertaken in Guatemala under the

direction of Dr. Diaz with the assistance of Dr. Ochoa and Mr. Owen Smith. On account of the difficulty in many instances of the surgical removal of the tumors, attempts were made to destroy the adult parasites in them by the injection of a number of different drugs. Table 1 shows the number of individuals examined and the percentage showing nodules. There is also indicated the different methods of treatment employed in 1935 and the results of this treatment as observed in 1936. The figures apparently indicate that the treatment employed in the sterilization of the tumors by the injection of several drugs has been fairly effective and that the rate of infection in 1936 was distinctly lower than it was in 1935. The rates of infection in these plantations in 1931 and 1936 are also compared in table 2. It is in Moca that the work of eradication has been specially prosecuted.

TABLE 1.—ONCHOCERCIASIS IN GUATEMALA

Number of Towns Visited, 176

1935

23,431 persons examined } 30 per cent infected
7,459 with tumours

1936 (first 7 months)

11,580 persons examined } 19 per cent still infected
2,205 with tumours

310 cases of Onchocerciasis, treated 1st July, 1935, re-examined 10th August, 1936

Tumors	Injected with violeta de genciana	Injected with hexyl-resorcinol	Total tumors injected
Persisted..........	58 (26.2 per cent)	38 (42.7 per cent)	96 (30.9 per cent)
Smaller...........	71 (32.1 per cent)	28 (31.5 per cent)	99 (31.9 per cent)
Disappeared.......	92 (41.7 per cent)	23 (25.8 per cent)	115 (37.2 per cent)
	221	89	310

TABLE

	Number of persons examined	Number of persons with tumors, 1936	Percentage with tumors, 1931
Moca.........	,279	295 (22 per cent)	40
Santa Adelaida	123	58 (47 per cent)	58.6
Pacayal.......	634	191 (30 per cent)	
Pacayalito.....	141	56 (40 per cent)	
Santa Emilia..	210	120 (52 per cent)	54

* *No figures available.*

A subsequent report by Diaz at the close of this campaign in 1936, concludes that the removal of the adult filariae, which stops the production of microfilariae, should be the foundation of anti-onchocercal therapeutics. He believes that injection of the tumors with the drug is the method of choice of killing the adult filariae, and at present, bichloride of mercury appears to be the most powerful drug for this purpose.

On the other hand, Sacre and Bustamente (1937), from experience gained in a five-year campaign against the disease in Chiapas, Mexico, prefer the removal by surgical excision of the tumors, because it eliminates the adult ones clearly, the results being controlled later by the absence of microfilariae. They feel that the killing of the worm

in the tumor by puncture, although more economical and less troublesome to the patient, is much less exact.

In Africa, D'Hooghe (1935) has recommended 0.5 to 1 cc. of a 5 per cent solution of thymol in carbon tetrachloride. He states that the injections are somewhat painful and he does not recommend the method for tumors situated about the cranium, which are dangerous ones in connection with ocular lesions, where surgical removal might be more certain in its effects.

Hissette has suggested thorough needling of the tumors with a large syringe needle to destroy the adult parasites. Many of the parasites are undoubtedly wounded or killed in this way, but the procedure is painful and not always certain in producing the desired result.

In Africa, where the disease in many localities is not sharply circumscribed, and in those in which the rate of human infection and of fly infection is very high, the eradication of the breeding places of the fly in the endemic regions constitutes by far the most important problem. Eradication of human infection in such districts would be entirely impracticable without the elimination of the fly.

Blacklock also has emphasized this fact. He admits, however, that the breeding places of the fly are not easy to attack. He enumerates raising the level of the water of streams, then lowering it again, scraping the channels, impeding the rate of flow in order to asphyxiate the larvae, and putting chemicals in the water, as measues which have been recommended. He also suggests as further methods to be tried, the clearing out of the streams in the dry weather, and attacking the breeding places when the water is low. He points out that Hissette advised the clearing of the ground for 500 meters from habitations and thinks that this would have been largely successful in the sort of locality where he was working in Sierra Leone, where the fly hid in the tall grass and did not seem to come at any long distance to attack. He thought that if that condition holds throughout the year, the clearing back of the bush and from the villages would result in a considerable reduction in the total number of bites.

Conditions of the spread of the disease vary greatly in different localities. It is not believed that clearing of the ground for 500 meters from habitations would materially influence the prevalence of the disease in Kassende, where very many of the infections evidently occur outside the village, in the fields and about the streams.

Gibbins and Loewenthal, with a wide experience in the study of *Simulium* in Uganda, where as high as 14 per cent of the flies were found infected, while admitting that suppression of *Simulium* is urgent, state that it is futile to attempt this by attacks on their breeding grounds. Gibbins (1936) has found that in Uganda the adults of this insect, *Simulium damnosum*, are capable of flying great distances. They twice raided Kampala, though local investigations appeared to have shown that there were no breeding places nearer than 45 miles away.

Indeed, in some localities in Africa it would appear that satisfactory eradication probably can only be accomplished by extensive sanitary engineering projects, and by the provision of a modern water supply for the district. Such changes as gradually occur in the building of modern residential centers should eventually result in the gradual extermination of the disease. By these and similar measures, the breeding places of the flies will be removed or gradually reduced, and the inhabitants

will no longer come into intimate contact with, and will not be exposed to, the bite of such flies. Such eradication apparently could be accomplished were the financial cost not considered to be too great to justify it.

Eosinophilia in Filarial Infections

Eosinophilia.—The origin of the eosinophilia which we have noted in some forms of filariasis is of interest. It is usually present in onchocerciasis, and is commonly over 30 per cent. The reason for this parasitic eosinophilia is not accurately known. It may also occur in infections with *Loa loa* and less uniformly with *Wuchereria bancrofti*, also at times in *Dracunculus* infection. Likewise, it may be present in other nematodal infections, particularly with *Ancylostoma duodenale* or *Trichinella spiralis*.

Blacklock points out that eosinophilia seems to be an attempt on the part of the host to neutralize some toxic substance produced, for example, in numerous helminthic infections, diseases of the skin and in asthma. There is some evidence that eosinophilia may occur as a protective action against foreign proteins, and it may be produced by the injection of many foreign proteins. That eosinophilia results from the presence of a foreign protein in helminthic infection is suggested by the fact that it may be most marked in active echinococcus infection when the hydatid cyst has ruptured or is leaking. On the other hand, when the cyst dies and becomes calcified, then the eosinophilia may disappear and the Cassoni test and the complimentary fixation reaction becomes negative. The repeated injection of a foreign protein causes tissue eosinophilia at the site of the injection. The fact, however, that the eosinophilia occurs especially after repeated injections and after a latent period suggests it is an allergic response.

The eosinophilia present in *Loa loa* infection associated with calabar swellings, which swellings occur in the course of this infection, is also apparently anaphylactic in origin. Chandler (1930), by the injection of a foreign protein (*Dirofilaria* antigen) into a patient infected with *Loa loa* was able to obtain a typical calabar swelling. Fulleborn (1932) finally confirmed this. Fairley also (1932), after a further study of skin tests in loiasis, has concluded that the calabar swellings essentially arise from a local anaphylactoid reaction involving the cells of the sub-cutaneous tissue not primarily of the dermis. The lesions of the skin referred to in onchocerciasis, where microfilariae and tissue eosinophilia are usually present, also probably represent in especially susceptible individuals an allergic response to foreign protein furnished by either the adult parasite or the microfilariae. The occurrence of eosinophilia in anaphylactic attacks of other origin (Theobald Smith phenomena) is, of course, well recognized. It is also well recognized that the injection of histamine may cause marked constriction of the bronchioles of the lung and give rise to asthmatic attacks, and also through its action on the adonomic nervous system may cause a dilation of the arterials and capillaries. Also, histamine entering the blood from the tissues may sometimes cause anaphylactic shock.

Code (1939) has reported that the eosinophile is the carrier of histamine and that histamine is transported in the body by the eosinophile, and that the presence of histamine in such cells may partly explain the mechanism which is present in asthma, hay fever and other allergic conditions.

Finally, in *Dracunculus* infection, as Fairley and Liston have found in the study of 125 cases, a few hours preceding the development of the local cutaneous lesion indicating the desire of the gravid female parasite to perforate the skin and to give birth to the enormous number of embryos with which the uterus is engorged, pronounced prodromal systemic symptoms appear, consisting of erythema and urticarial rash with intense pruritis, nausea, vomiting, diarrhoea, severe dyspnoea, giddiness and syncope, all believed due to toxaemia resulting from activation of the female worm. In a few hours the local papulo-vesicular lesion develops. These systemic symptoms together with an eosinophilia obviously simulate those observed in histamine poisoning. Moreover, they may be relieved by the administration of adrenaline. Therefore it would appear that there is considerable evidence in favor of the idea that eosinophilia in filariasis occurs especially in connection with an allergic reaction.

Myers and Kouwenaar (1939) and Bonne have observed in a number of cases swelling of the superficial lymphatic glands in filarial infection with hypereosinophilia especially in the lymphatic glands themselves. In two of Myers 7 cases there was bronchial asthma and in two a haemorrhagic nephritis. It was suggested that these two symptoms, together with the eosinophilia, may have a common allergic origin brought about primarily by the filarial infestation.

Dracontiasis

Definition.—Dracontiasis may be defined as an invasion of the connective tissues by *Dracunculus medinensis.* The adult female parasite, arriving at the surface of the skin, produces a local lesion and systemic manifestations, especially indicated by urticaria. Serious septic cellulitis sometimes follows rupture of the parasite. The infection is transmitted by species of *Cyclops.*

History.—*Dracunculus medinensis*, also known as the Medina or Guinea worm, is the oldest known Filaria (*Filaria medina*, Velsh 1674; *Filaria medinensis*, Linnaeus 1758); in fact, it has probably been known longer than any other human parasite. In early literature it was termed the serpent or dragon worm.

It appears to be referred to in the Bible by Moses (Chapter XXI of Numbers), as the fiery serpents that molested the Israelites in their sojourn on the shores of the Red Sea. Moreover, it was suggested that Moses taught the Israelites how to extract the worm by winding it around a piece of stick. The term *Drakontion* already occurred in the writings of Agatharchides, 140 B.C. Plutarch, Galen and Leonides likewise referred to this condition, and it was well recognized by Paulus Aeginus and Avicenna, who in addition described the method of extraction. Pigafetta (1598) also evidently observed and illustrated infection with this parasite in his account of his voyage through the Congo.

Geographic Distribution.—Infection is still present in Africa, where it existed in ancient times. The endemic centers include the Nile Valley, Arabia, both the interior and along the Red Sea coast, Uganda, central equatorial Africa, the borders of Lake Chad, the west coast of Africa from Mauritania to Gabun, Persia, Turkestan, India, comprising various localities on the west coast, especially around Bombay, the Central Province, parts of the Northwest Province, and parts of the Madras Presidency, particularly to the west of Madura. Chopra (1936) states that in the eastern half of India it is comparatively rare or absent. Infection has also been introduced into the islands of the Caribbean, the Guianas and, according to Campos, tȯ a limited area in south Brazil. Formerly it was said to be endemic in Curacao, Demerara, Surinam and Fiji. Brug states there are only two doubtful indigenous cases that have occurred in the East Indies. Connell and Buchanan have reported one case acquired in Tanganyika.

In the United States Chitwood, (1933) found reports of 10 cases of infection with *Dracunculus medinensis* in man. Four of these were either certainly or possibly of foreign origin, and 6 were cases in which infection with this parasite was more or less doubtful. Nevertheless, Chitwood points out that a species of Dracunculus occurring in the fox, racoon and mink in Nebraska, Iowa, New York, probably Pennsylvania and Ontario is morphologically identical with *Dracunculus medinensis* and probably is this parasite. Benbrook has also found *Dracunculus medinensis* in the fox in the United States. However, owing to the method of transmission of the disease and the public health conditions existing in the United States, man is not likely to become infected here. *Dracunculus medinensis* has also been reported as a natural infection in dogs, horses, cattle, the wolf, leopard, polecat, gibbon and baboon from the old world.

Distribution in the indigenous areas is very patchy. In India, for example, apart from the hill regions, the incidence per 100,000 prisoners varies from 6 in Bengal to 3,964 in Mysore and West Madras (Lane and Low). In the Colaba district of Bombay, Pradhan found 10 per cent of the population suffers annually, while in parts of the Deccan at certain seasons of the year nearly half of the population is affected, and in places on the west coast of Africa, nearly every Negro has one or more specimens about him (Manson-Bahr, 1938).

Mirza found that dracontiasis occured in about 95 per cent of the population of Shorapur, a town of 15,000 inhabitants in the southwest part of the Nizam's Dominions.

Description of the Parasite.—*Dracunculus medinensis* (Linnaeus, 1758; *Fullebornius medinensis*, Leiper, 1926) is classified in the subfamily DRACUNCULINAE (Stiles, 1907), family DRACUNCULIDAE (Leiper, 1912). In this family the females are enormously larger than the males and the anus and vulva are atrophied in the gravid female. In the genus *Dracunculus* the parasites have a cephalic shield, and the vulva is situated near the head.

The adult female lives in the subcutaneous connective tissue and at times may invade deeper layers. It measures on an average about 1 meter in length (75 to 120 cm.), by only 1.5 to 1.7 mm. in thickness, being a thread-like, cylindric, milky or yellowish white nematode. It is bluntly rounded at the anterior extremity, and recurved ventrad at the caudal end, which serves to anchor it in the tissues. The cuticulum is smooth. The anterior extremity possesses a cuticular thickening or oval shield. The minute, triangular mouth lies in an oval or quadrate prominence, and is surrounded by four pairs of papillae. A pair of lateral cervical papillae is found just behind the plane of the nerve ring, only 1 mm. from the anterior end. The mouth opens directly into the narrow oesophagus which merges with the glandular oesophagus just in front of the cervical papillae. The latter is continued into the cylindrical mid-intestine, which empties by a short conical rectal opening through a very minute aperture, often very difficult or impossible to detect. Nearly the whole body of the mature female is occupied by the uterus, which is packed from end to end with coiled-up embryos. The vagina, like the anus, also is not distinguishable and apparently becomes obliterated in the mature worm after she has become impregnated, and the vulva does not function at the birth of the larval microfilaria. According to Looss, the uterine tubes open into the posterior part of the oesophagus by a common duct, the oesophagus prolapsing

through the mouth at the time of parturition and being withdrawn subsequently. Leiper, however, believes that the worm discharges its young by prolapse of the uterus, and that this does not occur through the mouth but by rupture just outside the circumoral ring of the papillae that possibly may represent the vagina.

Until recently, little that was definite had been known about the adult male of the human species. As it had not been discovered in man, it was suggested that it disappeared soon after impregnating the female. A single mature male worm measuring 40 mm. was said to have been obtained from a natural infection in India, while Leiper (1906) in Africa fed to a monkey *Cyclops* containing presumably infective larvae of *Dracunculus medinensis*. Six months later Daniels found within it 5 immature worms, 2 males and 3 females. These worms were placed in the Museum of the London School of Tropical Medicine, but apparently no descriptions of them were published.

Fairley performed experiments upon 22 monkeys, *Macacus sinicus*, which were fed infected *Cyclops*, but without success.

Brug, who infected Cyclops with the larvae of the guinea worm, fed these to a gibbon (*Hylobates leuciscus*). More than a year later the apparently uninfected gibbon was killed and a full-grown female *Dracunculus* was found in the left calf, but no male was obtained.

Elucidation of the life history of *Dracunculus medinensis* in man resulted particularly from successive studies of other species of related parasites which infect animals (*Ichthyonema sp. Philometra sp.*, and *Dracunculus globocephalus*). In *Dracunculus globocephalus*, which infects the snapping turtle, (*Chelydra serpentina*) the male parasite has been found by Mackin (1927–28). It is very small in comparison to the female, the largest male measuring 20 mm. in length, while the largest female was 133 mm. The females were also from two to three times as thick as the males. The male has two spicules. The right has the form of a long narrow needle and was always found extruded from the genital cone for more than one-third of its length. In the female, evidences of a vagina and vulva in young females was detected, and Mackin believes it is probable that the vagina and vulva atrophy in females which have fully formed young.

Strassen also, from a careful study of *Philometra globiceps*, has been able to demonstrate in the young females a distinct vagina, though very narrow and often detected with difficulty. His studies of the fertilized adult female, on the other hand, showed that all traces of the vagina and vulva had disappeared. In a young female specimen he was able to demonstrate in section a portion of the spicule of the male in the vagina of the female.

Moorthy and Sweet (1936–38) have finally been successful in infecting dogs with the human species. The dogs were infected by feeding them infected *Cyclops* containing the embryos from man. The *Cyclops* were first infected with larvae taken from man by spraying newly opened guinea worm blisters with ethelchloride. Moorthy, in some 30 inoculations, was able to infect all six dogs, and in these he found 47 male and 181 female guinea worms.

The longest female was 53 cm. The maximum length of a male was 2.4 cm. It is noteworthy that no males were found when the infection had reached the age of six months. Hence it is believed that impregnation must take place in the early months and that the male subsequently disintegrates. The vagina of the female contained a mucoid plug when the female had reached 24 cm. As the length of the full grown female in human beings is in the neighborhood of 100 cm., it is evident that in the dog the females had not reached their full growth. With one dog, 350 days after the first infected feed, a temperature of 104° developed and a pea-sized blister appeared above the paw of the left hind foot. When opened and sprayed with ethyl-chloride, embryos appeared. Other worms showed themselves in other portions of the body. In some of the dogs, only females were found and no males.

The larvae of *Dracunculus medinensis* do not circulate in the blood or lymph in man; they remain in the body of the parent worm and are only set free at the time of parturition, usually when the head of the worm is brought into contact with water, or when rupture of the worm may occur in extraction. In clear water they may remain alive for six days; while in muddy water or moist earth they may live from two to three weeks. If slowly and partially desiccated they may not die, but may later be resuscitated by moisture.

The larvae have no boring apparatus or means of passing through tissues, or even of entering the integument of their intermediate host, *Cyclops*. They are filiform, measuring 550 to 750μ in length by about 17μ in breadth, and move rapidly with a somewhat tadpole-like motion. The movements are intermittent, sometimes short

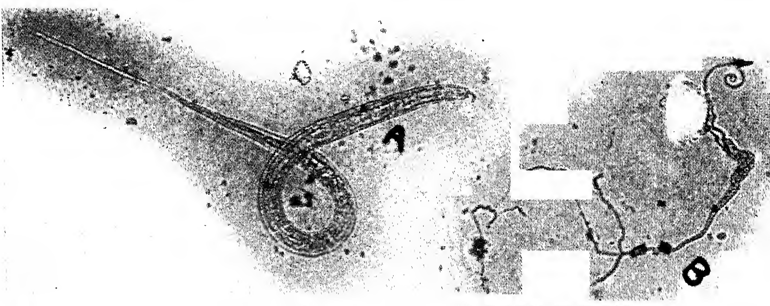

FIG. 323.—Fresh *Dracunculus medinensis* larvae treated with the fixative solution; *A*, *Dracunculus* larva that is just vomiting the oesophagus; *B*, vomited portion of the entire oesophago-intestinal region of the larva. (After Moorthy.) (Courtesy Jl. of Hygiene.)

spasms producing a form like the Greek α, alternating with brief pauses, and straightening. The anterior end is bluntly rounded and the caudal process is long and attenuated. In fixed specimens it may be seen that the oesophagus is bulbous and the mid-intestine, anal pore, nerve ring and genital primordium may be recognized, as well as a pair of anal papillae, set into deep pockets, one on either side of the anal opening. The cuticulum is conspicuously transversely striated.

Transmission.—The method of infection of man is quite different from that of the other Filariidae described, and there is no insect host. As the cephalic end of the adult female approaches the human skin, a papule is formed in the dermis which shortly after becomes vesicular. Shortly after, this blister ruptures and if the part comes into contact with water, (which it is apt to do as the patient often thrusts the part into water to relieve the burning sensation in it), the head of the parasite is thrust out through the opening of the skin. A prolapse of the uterus of the parasite then occurs through the ruptured anterior wall of the mouth and repeated discharges of motile, first-stage larvae take place into the water.

The manner of transmission of this parasite to man as well as certain other features of the life cycle, was suggested by the study of allied species in fish. Leuckart had

observed that the larvae of *Dracunculus* resemble those of *Cucullanus elegans*, a parasite of *Perca fluviatilis*, and that the nature of parturition was similar in these parasites in that the larvae can reach the open only after the bursting of the uterus or body of the mother, which occurs particularly when contact with water is secured. The embryos then escape and live for from about three to ten days, swimming in the water. In consequence of this similarity, and because the larvae of *Cucullanus* were known to develop in *Cyclops*, Fedschenko (1870) acting on the advice of Leuckart, introduced the larvae of *Dracunculus* into water containing *Cyclops*, the larvae of insects, etc., and was able to observe the invasion of the *Cyclops* by the larvae. About the twelfth day the parasites moulted and assumed further development. They could be observed within the *Cyclops* until about the fourth week by which time they had grown to a length of 1 mm. An attempt to infect young cats and dogs with the larvae, by giving them infected *Cyclops* in milk or water, failed. Manson, and also Blanchard, confirmed Fedschenko's observations of the development of the parasite in *Cyclops*. Fedschenko

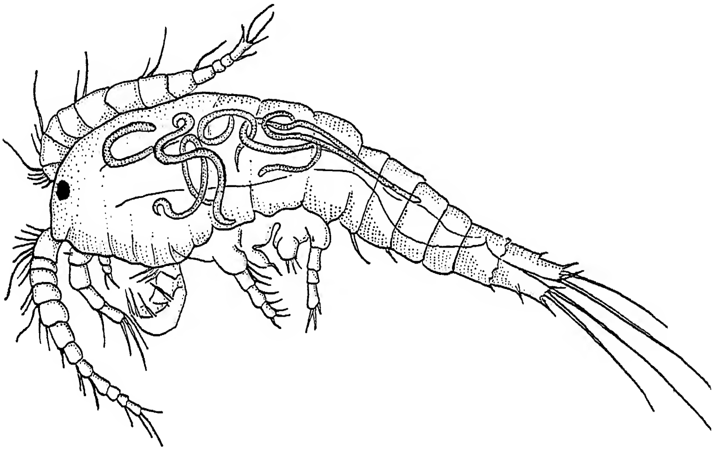

FIG. 324.—Cyclops containing larvae of Dracunculus medinensis.

thought the parasite in infected *Cyclops* bored its way through the integument of the body. He did not observe the passage of the parasites into the mouth of the *Cyclops*. However, Nybelin has published experiments which show that in a closely allied species of the genus *Philometra*, *Filaria sanguinea* infection certainly does occur *per os* and not through the integument of the Cyclops. After ingestion, however, by the *Cyclops*, the parasite promptly bores its way through the walls of the alimentary tract into the body cavity, where its further development occurs. Moorthy (1932) in India, has also confirmed the infection of *Cyclops per os* with *Dracunculus medinensis* larvae. In the body cavity of the *Cyclops*, ecdysis occurs. The entire metamorphosis of the larvae may, in some instances, be completed in from ten to twelve days.

Nevue-Lemaire lists the following species of Cyclops as satisfactory for the development of *Dracunculus*: *C. quadricornis*, *prasinus*, *viridis*, *serrulatus*, *strenuus*, *bicuspidatus*, *coronatus*, *leuckarti*. Faust says there are probably other species concerned, also.

Leiper showed that when an infected *Cyclops* is transferred to 0.2 per cent solution of hydrochloric acid, in other words an artificial gastric juice, it is immediately killed, but the larvae are not destroyed and are aroused to greater activity, escaping from the *Cyclops* and swimming about freely. It was hence conjectured that under natural conditions man becomes infected through the ingestion of *Cyclops* containing this

filaria, the gastric juice acting on the *Cyclops* and the parasites in the same way as the hydrochloric acid in the experiment.

In order to prove this, Leiper fed a monkey on bananas concealing *Cyclops* which had been infected for 5 weeks, and which contained fully-developed larvae. Six months later, when the monkey died, 5 worms were found in its connective tissues, all possessing anatomic characteristics of *Dracunculus medinensis*. These experiments were repeated on 22 monkeys, *Macacus sinicus*, by Fairley and Glen Liston, who failed to confirm this work of Leiper. However, Brug has been able to infect a gibbon by feeding it infected *Cyclops*, and to obtain after a year the adult female parasite. Fairley and Liston have also produced the disease in man in one instance by feeding infected *Cyclops* and Moorthy has infected dogs by feeding them infected *Cyclops*.

The evidence then would appear to be conclusive that man becomes infected by ingesting infected *Cyclops* in drinking water, and that the action of the digestive juice causes the larval forms of the parasite to free themselves and to later penetrate the walls of probably either the stomach or duodenum. They then migrate through the tissues, where the developed male and female worms come to lodge in the subcutaneous connective tissue. A period of ten to fourteen months is required before the female worms are mature and are ready to discharge their young.

While the paucity of male worms has not been entirely explained, it has been suggested that after the male fertilizes the female it dies and disappears. However Faust has suggested that it is possible that the females do not even require fertilization to produce viable progeny.

Clinical and Pathological Features

The female, on attaining maturity, travels most commonly toward the legs and feet. It is said to be in conformance with her instinct to seek water. These are the parts of the human body, of natives who wear no shoes, most likely in tropical countries to come in contact with puddles of water, the medium in which *Cyclops*, the intermediary host, lives. Manson said that the water-carriers in India are subject to guinea worm, which in their case is prone to appear in the back, that is, the part of the body against which the water-skin lies when being carried. However, in 85 to 90 per cent of the cases the female presents itself in some part of the lower extremities. Occasionally it is observed in the scrotum, also rarely in the arms or other parts of the body. Rao observed an adult guinea worm in an abscess of the scrotum of a child aged 2 years.

Riou found, in a case in which the adult worm had produced adenitis, an abscess of the right inguinal gland. Upon puncture of the gland, larvae were found free in large numbers in the aspirated pus. Later the adult parasite was removed from the gland.

Forbes's statistics of the point of appearance of the head of the parasite beneath the skin give 77 per cent legs, 22 per cent feet, 9 per cent arms and hands, 4 per cent abdominal wall, 4.5 per cent scrotum, 3.5 per cent back and buttocks, 1 per cent eye, and 1 per cent penis. According to Fairley, in 140 persons who harbored 266 guinea worms, the parasite appeared at the surface of the skin in the leg in 218, in the arms in 15, in the back in 11, in the buttocks in 5, and in the scrotum in 4. Clarac has reported one instance in which the worm appeared in the tongue. Wright observed one case of a calcified

guinea worm in the orbit, and Noronha one case in the region of the eyes, displacing the eyeball. In the few other instances of reports of infection of the orbit, the parasite may have referred to a different species.

Symptoms.—During the period of incubation, from 10 to 14 months, during which time the worm reaches the adult stage, there are generally no apparent symptoms. Lane and Low state that in some instances there may be indefinite pains in the limb in which the parasite lies, and aching sensations may be complained of, and a feeling as if there was a cord under the skin is also described. The onset of the symptoms usually occurs a few hours previous to or at the time when there are manifestations of the appearance of the worm near the surface of the skin. The prodromal symptoms consist of local erythema, sometimes of slight fever and other systemic manifestations, especially generalized urticaria, intense itching, nausea, vomiting and diarrhoea, severe dyspnoea, asthma-like symptoms, giddiness, and even syncope. These symptoms are

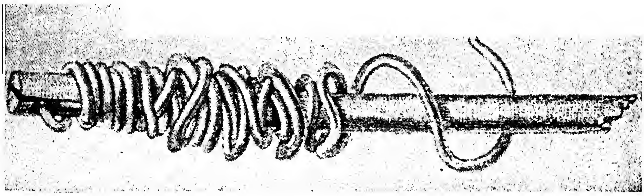

FIG. 325.—Guinea worm. Rolled on a stick for gradual extraction. (From Greene's Medical Diagnosis.)

believed by Fairley and Liston to be due to toxic secretions of the worm which are given off particularly at about the time of its parturition, and which are absorbed in the system of the host. These preliminary symptoms may resemble histamine poisoning. They vary greatly according to the susceptibility of the patient. The localized lesions usually become evident a few hours after the onset of the systemic symptoms, but at times they are coincident with them. Especially when the head of the worm comes to the surface, or points, an itching, burning, boring, or dragging sensation is experienced at the spot pressed upon. If the patient has before harbored a guinea worm that has been removed, he can usually tell when the worm is coming to the surface. A small group of papules or a single one usually now become visible, and gradually in the center of this area the epidermic becomes elevated and a small vesicle forms. The inflamed area increases somewhat in size during 24 to 48 hours. The irritation produced often causes the patient to immerse his foot in water. This vesicle and its margin, which gradually becomes more indurated, may cover an area of from 2 mm. to 5 or 6 cm. in diameter. Later on the blister, if not opened, usually ruptures disclosing a small erosion and a small perforation, large enough to admit an ordinary probe, is visible. Sometimes the head of the worm is seen protruding from this opening. If this is not so and the opening is douched

with a stream of cold water expressed from a sponge, in a few seconds a drop of somewhat milky fluid often exudes and flows over the surface.

Sometimes instead of this fluid a small tube, which is the uterus of the parasite, may be projected through the hole in response to the stimulus of the cold water. Apparently in this act the tissues of the head are often ruptured. When the uterus of the parasite has been extruded about an inch, it suddenly fills with an opaque whitish material, ruptures and collapses, the fluid spreading over the surface of the erosion. If a little of this fluid is placed under the microscope, it is seen to contain myriads of *Dracunculus* larvae, and if a drop of water is added to them they may be observed to swim actively about. If the wound in the patient is again douched with cold water, after an hour or so a fresh supply of larvae can be obtained, and this process can be continued from time to time until the worm has emptied herself. Apparently the cold water applied to the skin stimulates the worm to contract and thereby forces out her uterus little by little until it is completely extruded.

The toxic symptoms usually subside upon rupture of the vesicle and the appearance of the head of the worm in the base of the lesions. However, following this, the region around the worm often becomes extremely painful, inflamed and oedematous, and cellulitis, due to secondary bacterial infection, may result. Some of the cellulitis, may be due to the excretion of toxins by the mature parasite, as Fairley and Liston found from experimental laboratory inoculation of animals. However, in their study of 218 human cases, they found that all the more serious complications are connected with secondary bacterial infection. In 71 per cent of the cases, the blister had ruptured at the time the patients presented themselves for treatment, and in 43.7 per cent septic complications were already established. Nevertheless, they also encountered aseptic abscesses which in some instances they believed were caused by the embryos of the parasite.

Botreau-Roussel and Huard have likewise described non-bacterial inflammation around joints, and have emphasized the aseptic character of the purulent material in a series of cases of infection with *Dracunculus* complicated by synovitis. They emphasize the disturbances of the knee joint that may occur from the presence near it of *Dracunculus*. Pain, redness and swelling often occur in the region of an invaded joint with later effusion.

Pradhan points out that in India, near Bombay, in 23 per cent of the cases of Dracunculus infection a joint is affected (generally the ankle) which often leaves a permanent and crippling condition. Journe reports a case of septic arthritis of the right knee joint while the skin was intact. The joint was incised and cocci were present in the fluid. A month after the primary incision, a guinea worm presented through the wound, having presumably been instrumental in introducing the bacteria. Later, ankylosis of the knee joint followed.

When the worm presents in the lower part of the leg or foot, the part usually swells more or less, and becomes red and tender, and walking becomes impossible. Bauvallet states that in north French Africa, dracunculosis cripples about 7 per cent of young porters.

Deeper lesions caused by the parasite and secondary infection from staphylococci and streptococci which sometimes ensue, produce conditions such as sloughing of the tendons, periostitis, necrosis of the bone, gangrene, and general septicaemia, from which death may result. Lane and Low report cases of the worm passing into the scrotum, where a funiculitis may be set up and, if the bacterial infection is superadded, serious epididymitis and orchitis, with ultimate destruction of the testicles, may occur. They point out that if the parasite comes to the surface in the orbit, the eye may be destroyed, or if in the breast, a mastitis or mammary abscess may supervene. In the instance reported by Noronha a baby girl, aged 6 months, had had for 4 months frontonasal tumors on each side, the size of a walnut, and showing inflammation and displacing the eyeball outward. They were first diagnosed as dermoid cysts. Dissection of one of

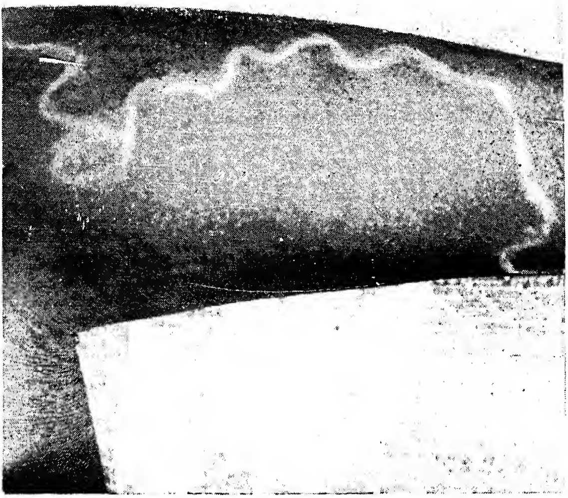

FIG. 326.—Female guinea worm lying under the skin of the forearm. (By permission from Manson's Tropical Diseases.)

the tumors was followed by the child's death. In the center of the tumor the coiled adult worm was found.

In some instances the worm fails to come to the surface and pierce the integument, or it may die before reaching maturity, if no sepsis is associated it may become absorbed or calcified, and in some instances be felt as a hard cord beneath the skin, or an abscess may result. In other instances, the calcified worms may give rise to sciatica, synovitis, and periostitis.

Diagnosis.—Diagnosis may only be possible when the adult parasite presents itself at the surface of the skin. In other instances it has occasionally been made when on opening abscesses a complete adult parasite or portions of one have been encountered. In aspirating an affected joint, the larval forms are sometimes found in the fluid removed. Lester found in one instance an entire adult parasite contained in a hernial sac.

Roentgenograms may be of service in detecting the location of the parasites, particularly when they are effete or calcified, and their presence in the part is suggested. Injections of lipiodol or collargol into the worm renders it opaque, and often its exact position in the tissues may then be determined by subsequent skiagraphy. Eosinophilia of varying degree is usually present in the blood. Lane found that 13 per cent was an average count. However, in some instances of infection there has been no increase in the eosinophiles in the blood.

Ramsay (1935) has employed the intradermal test for dracontiasis, using the saline extract of the parasite. He reports that 47.6 per cent of the persons gave a positive reaction. However, some of the positive reactions occurred in persons who declared that they had never been infected with guinea worm. Ramsay failed to produce an antigen which gave a satisfactory precipitin test.

Prognosis.—The prognosis, on the whole, is good. Frequently only one *Dracunculus* is present, and if it is carefully removed there is often no further trouble. However, multiple infections are not uncommon.

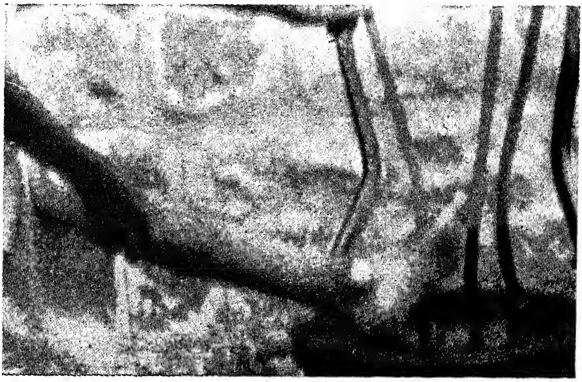

FIG. 327.—Dracontiasis patient; the blister is seen just forming near the ankle. (After Moorthy.) (Courtesy Journal of Hygiene.)

Fairley and Liston found the average number of worms per person was 1.9. Bauvallet found that infection was generally multiple in Africa, and in one instance the patient had suffered at intervals from infection with 8 of the adult worms. Gore who in Hong Kong observed 11 cases which had contracted the infection in India, found that 10 had plural infections; 8 worms were removed from one man, 5 whole, and 3 broken. Cellulitis and abscess developed in these three. Fulleborn says that cases in which ten worms have been present at one time are not very rare.

When serious sepsis has occurred, the results may not be so good, and when the parasites are located near the joints, permanent deformities often result. Pradhan, who found 10 per cent of the Coloba District of Bombay suffering yearly from guinea worm infection, found that in 23 per cent a joint was affected, leaving a permanent and crippling condition, so that the economic waste was considerable.

In a number of countries the amount of temporary disability caused among troops has often been very serious. The lesions are aggravated by marching and by the use of the limbs. In many instances, the men are incapacitated for military duty until the parasite has discharged her larvae and the lesion has healed, a process which takes on the average about a month.

The danger of reinfection in endemic centers is also often great. Moorthy points out that in the Chitaldrug District in Mysore, India, of

1363 sufferers from dracontiasis in one year, 1144 had previously been infected.

Treatment.—As soon as the detection of the guinea worm has been made by its appearance at the surface of the skin, it is advisable either to place the patient in bed or to obtain rest for the affected extremity or part. Much of the disturbance that results is sometimes due to the fact that the patient continues to use the limb, which favors swelling and other inflammatory changes, and hence secondary infection with bacteria.

When systemic symptoms are present, with urticaria, pruritis, dyspnoea, and nausea, the administration of adrenalin may give relief.

Probably the most successful method of treatment is the one practiced in ancient Biblical times, modified by our improved knowledge of the habits of the parasite and the value of antiseptic treatment. If seen before it has ruptured, the blister should usually be opened aseptically with scissors, and any necrotic skin around the opening excised. If the guinea worm is protected from injury and the part occupied frequently douched with water, often the uterus will be gradually forced out and emptied of embryos. Until this process is completed, the worm resists extraction and the hook at the end of the tail assists it to maintain its hold in the lesion. When parturition is completed, generally in from 15 to 20 days, the worm is often gradually absorbed or tends to emerge spontaneously.

During the process of parturition of the worm, the lesion should be covered with a sterilized pad of gauze, kept moist with sterile water and covered with protective rubber. The dressing should preferably be removed twice daily, and cold water dropped on the limb above and around the lesion to hasten the discharge of the larvae. As soon as the worm protrudes sufficiently from the opening, a small piece of silk thread should be tied to it and the end of the worm fastened by the thread to a small piece of bamboo or other wood. An attempt should then be made to extract the worm by obtaining slight traction through making a turn or two of the stick daily. Care should be taken not to exert much force or to withdraw the worm too soon, as the worm is liable to rupture, and inflammatory changes and cellulitis then generally result. It is on account of this danger of rupture of the parasite that some physicians have advised abandonment of this old method of extraction.

If, however, the extraction is performed slowly, the results appear to be more satisfactory on the whole than with other methods of treatment. However, Moorthy (1942), who has had experience during many years in treatment says that this old method is the one which is still employed in most of the villages. In many localities there is still used the application of cold poultices made from the tender bamboo shoots. It has been observed that when this poultice is applied after opening the blister, the worm is induced to dislodge itself from the tissues and issue from the skin opening and liberate the larvae in enormous numbers into the poultice. The advantage of this method over the application of only a cold pad or supplying the effected part with ethyl chloride is that the liberated larvae are immediately killed by the hydrocyanic acid and another toxic principle found to be present in an aqueous extract of young bamboo shoots. Bauvallet, who has employed the old method in a routine way, gives the average duration of such treatment as twenty-three days. The longest time was 73 days, and the shortest (upon an oprative case), 11 days. In this one operative case— a patient who had previously had 7 parasites extracted from his legs—the eighth *Dracunculus* presented itself in the skin over the thorax at the level of the eighth rib. The parasite was extracted whole through a wide incision and careful dissection. Bauvallet points out that this method of treatment is not recommended in general, and should be applied only in a case where the parasite is well localized and coiled about itself. This method of surgical treatment, however, shortened the time of indisposition of the patient to only 11 days.

A number of authors have suggested surgical dissection of the worm. Fairley and Liston have recommended that after the parasite has been located by making it prominent and palpable by applications of ice or ethyl chloride, which is said to induce contraction of its musculature, 2 or 3 small incisions are made across and over the length of the worm, loops are pulled out with a strabismus hook, cut across, and the pieces withdrawn through these openings and the sinus; the latter after extraction of the pieces being disinfected with a 1:30 carbolic solution. However, they advise actual excision of the worm when it lies convoluted in a limited space; but if this is not the case, they recommend intermittent traction combined with massage.

A number of drugs have been recommended to destroy the parasite. Macfie, Fairley and others have employed injections of tartar emetic intravenously; Jeanselme and Montpellier, novarsenobenzol; and Chaigneau and Tournier, "Kermas" (tersulphide of antimony). More recent observations appear to indicate that such methods of treatment have little value. Others have suggested injection of the worm with chloroform or cocaine in order to kill it. Injection of perchloride of mercury directly into the worm has also been recommended for the purpose of destroying the parasite or rendering it sterile. The difficulty of this method lies in inserting the point of the needle into the body of the worm, and even if this is done one cannot be sure that the fluid will penetrate the entire length of the worm. Lane and Low state that in their experience the method has not proved successful, the older one of winding the parasite about a stick having given better results. Moorthy (1933) states that injections of perchloride solution in a strength of 1:1000 have been reported to give good results in parts of India, but it has been difficult to persuade the majority of the villagers to adopt this method on account of the severe local pain and irritation caused by the drug. He recommends instead injections of acriflavin solution, 1:1000, which he states is used with success in certain cases. This drug appears to have some advantage over other preparations. No local pain or irritation is produced, nor does it give rise to any other systemic disturbances. On the contrary, it seems to give immediate relief to the local itchiness and biting pain so frequently complained of. Neither Bauvallet or Morard (1933) recommend the method of injecting the parasite to destroy it. Nevertheless Elliott (1942) believes injections of phenothiazine is very satisfactory if the injection is given hot and carefully watched for toxic symptoms.

Moreover, Botreau-Roussel believes that he has conclusively demonstrated the inefficacy of the various drugs which have been employed for this purpose. He has found that by injections of lipiodol into the body cavity of the parasite, inserting the hypodermic needle into the extremity which points at the skin, that excellent radiograms, showing the location of the worm, may sometimes be obtained (see Fig. 329). These radiograms show that the worm is present in the connective tissue and not in the muscles. Hudellet has suggested injections of collargol in order that the worm may be located by roentgen rays and then dissected out. However, Botreau-Roussel's excellent roentgenograms of a number of cases show that such a procedure, on account of the tortuous curve and extensive ramifications of the worm, at least in many instances, is not advisable.

If cellulitis has already occurred when the patient comes under observation, strict rest must be enforced and antiseptic fomentations, such as lysol or carbolic solution in a strength of 1:40, should be freely applied. If the cellulitis is severe and shows a tendency to spread, incision should be made, and if there is pus it should be freely evacuated. Abscesses, which may form in the breast as well as in the extremities, should also be freely opened.

The condition of the joints may sometimes require surgical treatment. Botreau-Roussel and Huard have emphasized that aspiration of the joint and removal of the sterile pus is in many instances all that is required. However, Lane and Low state that in the more serious cases the infection may be such as to require opening and draining of the joint, and perhaps even excision.

During convalescence the limb should be used with care. In a few instances calcified worms may give rise to sciatica, and in such instances surgical removal after roentgen-ray demonstration may be advisable.

For the treatment of distressing prodromal symptoms such as urticaria and asthma, which may be due to the absorption of toxins from the worm,

Fairley and Liston have found that subcutaneous injection of about 10 minims of a 1:1000 solution of adrenalin hydrochloride immediately relieves such symptoms.

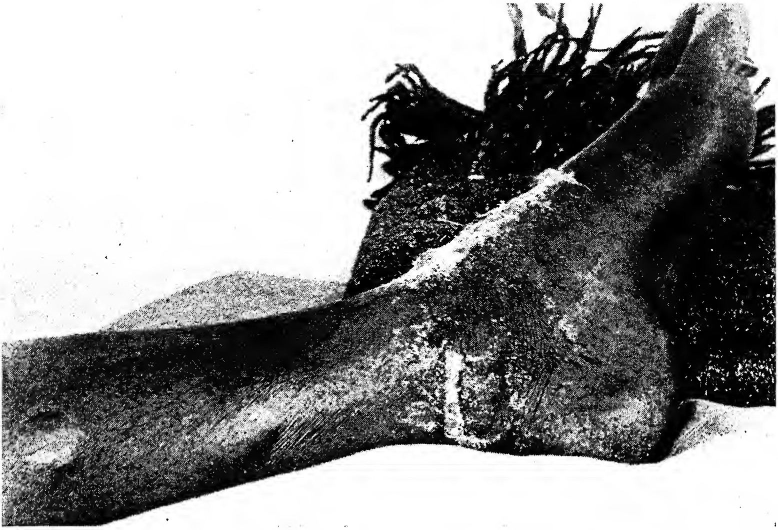

FIG. 328.—*Dracunculus medinensis.* Guinea worm extraction in India by the native method of winding around a strip of bamboo.

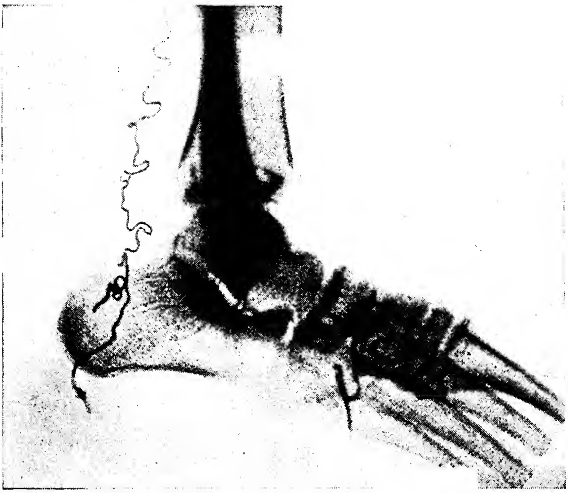

FIG. 329.—*Dracunculus* radiogram. (After Boutreau-Roussell.)

Prophylaxis.—Infection occurs only by drinking water containing infected *Cyclops.* In India, the wells approached by steps are the great source of infection, and in Africa, the ponds in the neighborhood of villages.

Prophylactic measures should include: (1) Prevention of the larvae of *Dracunculus* from reaching the water from wells by prohibiting the drawing of water from wells by those infected with the parasite and by covering of the lesion in which the worm is present by a surgical dressing and the subsequent destruction of the dressing. The wells and tanks approached by steps, and the other sources of water supply where individuals are able to stand in the water when obtaining the drinking supply, should be abolished as soon as possible and, instead, artesian wells should be substituted where practicable, and these and other wells provided with pumps rather than with buckets for drawing water.

(2) The killing of *Cyclops* in the wells. Leiper found that this might be effected in 6 hours in a well containing a thousand gallons by heating the water from 15 to 65°C., which implies the running into it during six hours of the steam obtained by the vaporization in a boiler of 87 gallons of water, and the consumption of 87 pounds of coal. However, Rogers has pointed out that this treatment would have to be performed weekly, and that the expense, in India at least, is prohibitive.

Killing of *Cyclops* in water has also been recommended by the introduction of chemical substances, especially such as caustic potash (Alcock), permanganate of potash (Turkhud), and lime, 80 per cent CaO (Pradhan).

Davis found in laboratory experiments that caustic potash, bleaching powder, potassium permanganate, quick lime and slaked lime, as well as several other substances in a pH of 10 or more, was lethal in all cases to the *Cyclops*. A convenient method of treatment of the water was suggested by adding quick lime or ordinary lime in the solution of 1:1000. Pradhan found in practical use that *Cyclops* lived for 24 hours in potassium per manganate, 2 oz. in 1,000 gallons of water, and points out that such water is undrinkable. Lime, 80 per cent CaO, in a strength of 1 drachm to the gallon, was used by removing water from the well and returning the water with the requisite amount of lime dissolved in it. The water was potable in two days. The process had to be repeated every fortnight, as the *Cyclops* appeared again after that period. In two villages in which the wells were so treated, a slight favorable effect was obtained in the reduction of the number of infections of the village which used the well. Moorthy has found that perchloron in combination with copper sulphate seems to give the best results in the destruction of *Cyclops*. However, he points out that of all the disinfectants tried, none kill the eggs of the Cyclops as effectively as they destroy adults, with the result that Cyclops invariably reappear in the well within a month or two of treatment.

Moorthy and Sweet have suggested, for the biologic control of the disease, the introduction of fish, *Barbus puckelli*. The fish are added one month after treatment of the water with perchloron. This fish has been introduced experimentally into some of the step wells in India. Laboratory experiments have shown that this species of fish feeds voraciously not only on *Cyclops* but also on the guinea worm larvae. In certain endemic centers in India, Liston and Turkhud found 37 per cent of the *Cyclops* infected.

Pradhan points out that since guinea worm disease is seasonal in India, the great mass of infections occurring between February and May, the use of lime for the disinfection of wells to prevent contamination of the water by acute cases need only be carried out during this period of the year.

(3) For personal prophylaxis, obviously boiling and filtering the drinking water is efficient for the destruction of the larvae and for preventing the infection. As the *Cyclops* are just visible to the naked eye, straining the drinking water through coarse calico, such as villagers use for clothing, has been suggested by Rogers as the simplest and most practical method for them to avoid infection.

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Chapter XLVII

DISEASES PRODUCED BY TREMATODES OR FLUKES: SCHISTOSOMIASIS

Zoological Considerations.—Flukes are non-segmented flat worms, usually leaf-like in outline, rarely cylindrical. They are characterized by the possession of suckers by means of which they attach themselves to the skin, mucosa, or other tissues of their host. With the exception of the SCHISTOSOMATOIDEA, all flukes are hermaphroditic, and their eggs

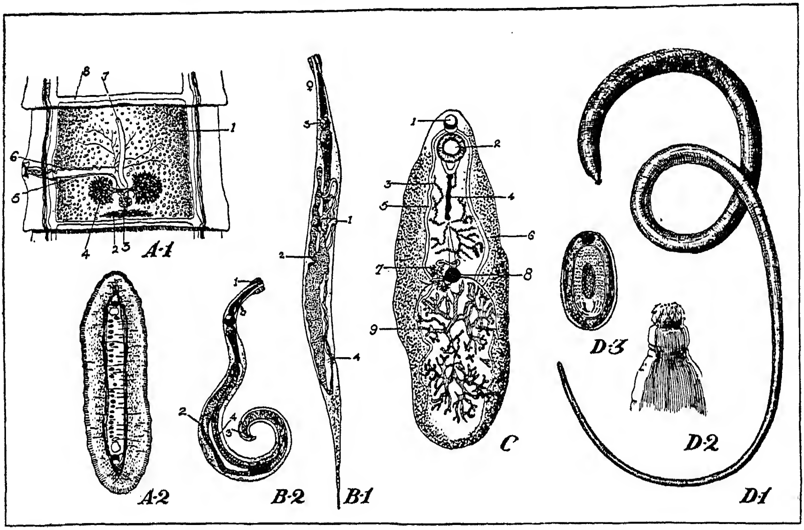

FIG. 330.—Illustration showing anatomical distinctions between a cestode, a nematode, a trematode and one of the Acanthocephala. A1. *Taenia saginata;* 1. Testes; 2. Yolk glands; 3. Shell glands; 4. Ovaries; 5. Vagina; 6. Vas deferens; 7. Uterus; A2. Cross section of same. B1. Female *Enterobius;* 1. Vulva; 2. Ovary; 3. Bulb oesophagus; 4. Anus; B2. Male *Enterobius;* 1. Oesophageal inflation. C. *Fasciolopsis buski.* 1. Oral sucker; 2. Acetabulum; 3. Uterus; 4. Cirrus pouch; 5. Intestines; 6. Yolk glands; 7. Ovary; 8. Shell gland; 9. Testes. D. 1, 2, 3. Worm, head and egg of *Macracanthorhynchus hirundinaceus.*

are operculated (provided with a lid). The only other operculated eggs met with in human infections are those of the DIPHYLLOBOTHRIIDAE of the class Cestoda.

Morphology.—These parasites vary in size from those just visible to the naked eye like *Heterophyes* and *Metagonimus* to large, fleshy species like *Fasciola* and *Fasciolopsis.* The most characteristic external structures of the flukes are the acetabula, or suckers. Flukes of medical importance have 2 suckers which, except in the PARAMPHISTOMOIDEA, are quite close together: an oral sucker surrounding the mouth at

the anterior extremity and a ventral sucker or acetabulum. The intestinal tract consists of a pharynx, proceeding from the oral sucker, which bifurcates and terminates in 2 blind intestinal caeca. In the SCHISTOSOMATOIDEA the branches reunite to end in a single caecum. There is no anus. The excretory system is bilaterally symmetrical and open at the posterior end of the body, usually on the dorsal aspect. It consists of numerous, scattered, cilated "flame" cells from which minute canaliculi arise. These unite to form 2 collecting ducts which join posteriorly in the excretory vesicle which discharges through the excretory pore.

The reproductive organs are extremely complicated. In a few species like the human blood flukes the sexes are separate, but the great majority are hermaphroditic. On the male side of the system there are usually 2 testes, which vary greatly in shape and position in different families. From each a vas efferens arises, and these unite. to form a vas deferens. This discharges at a genital pore, situated usually ventrally, near the bifurcation of the gut in front of the ventral sucker. The terminal part is often modified to form a muscular copulatory organ, the cirrus. In the female system there is a single ovary from which the oviduct arises. This gives off a branch which ends blindly in a receptaculum seminis, but which may give off a secondary branch (Laurer's canal) which opens externally on the dorsal surface and is believed to take care of the overflow from the oviduct. The oviduct proper, in which fertilization of the ova takes place, receives ducts from the yolk glands and the shell gland, and continues forward as the uterus. The uterus discharges the ova at the common genital pore. The terminal part functions as a vagina at the beginning of sexual activity, but after the uterus becomes filled with ova, copulation seems impossible.

Classification.—Flukes are divided into two subclasses: (1) the *Monogenea*, in which the egg gives rise to a larva which becomes an adult without an intermediate host; and (2) the *Digenea*, in which the larva first becomes parasitic in some intermediate (molluscan) host, and there gives rise to subsequent generations of larvae of which some final stage develops into adults in the vertebrate host, either directly or after having evolved further in one or more subsequent intermediate hosts. The flukes parasitic in man belong to the latter subclass.

The three important superfamilies of flukes parasitic for man are:

1. PARAMPHISTOMOIDEA—flukes with two suckers, one situated at each extremity. This includes the genera *Gastrodiscus* and *Watsonius*.

2. FASCIOLOIDEA—flukes with two suckers, one terminal, the other posterior to it and situated ventrally. This family includes the important genera *Fasciola*, *Opisthorchis*, *Dicrocoelium*, *Fasciolopsis*, *Paragonimus*, *Clonorchis*, *Heterophyes*, *Metagonimus* and *Echinostoma*.

3. SCHISTOSOMATOIDEA—flukes in which a leaf-like male, by an infolding of its sides, makes a channel for the thread-like female. The sexes are separate, not united in a hermaphroditic worm as they are in the Fascioloidea and Paramphistomoidea.

KEY TO THE IMPORTANT TREMATODES PARASITIC IN MAN
Superfamily FASCIOLOIDEA. Hermaphroditic. Eggs Operculated

Genital pore posterior to acetabulum.......... 1
Genital pore anterior to acetabulum.......... 2
1. Flukes minute, with a third (genital) sucker.......... *Heterophyes*
   Flukes medium in size, two suckers, eggs in sputum and faeces.......... *Paragonimus*
2. Intestine dendritic.......... *Fasciola*
   Intestine not dendritic.......... 3
3. Testes anterior to uterus.......... *Dicrocoelium*
   Testes posterior to uterus.......... 4
4. Testes branched.......... 5
   Testes lobed or entire.......... 6
5. Flukes about 4 to 7 cm. long, eggs 150μ.......... *Fasciolopsis*
   Flukes about 1 to 2 cm. long, eggs 30μ.......... *Clonorchis*
6. Flukes about 1 cm., no ring of spines, eggs 30μ.......... *Opisthorchis*
   Flukes 2 mm., no ring of spines, eggs 30μ.......... *Metagonimus*

Superfamily SCHISTOSOMATOIDEA. Sexes Separate. Eggs Not Operculated

Eggs 150μ, terminal spine, in urine (rarely faeces) .... *Schistosoma haematobium*
Eggs 150μ, lateral spine, in faeces (rarely urine) .... *S. mansoni*
Eggs 90μ, minute lateral knob, in faeces .... *S. japonicum*

CLASSIFICATION OF THE PLATYHELMINTHES (FLAT WORMS)

Class Trematoda

Superfamily	Family	Genus	Species
Paramphistomoidea	Gastrodiscidae	Gastrodiscus	G. hominis
	Paramphistomidae	Watsonius	W. watsoni
Fascioloidea.	Fasciolidae	Fasciola	F. hepatica
		Fasciolopsis	F. buski
	Troglotrematidae	Paragonimus	P. ringeri
			P. westermani
			P. compactus
		Troglotrema	T. salmincola
	Echinostomatidae	Echinostoma	E. ilocanum
	Opisthorchiidae	Opisthorchis	O. felineus
		Clonorchis	C. sinensis
	Heterophyidae	Heterophyes	H. heterophyes
		Metagonimus	M. yokogawai
	Dicrocoeliidae	Dicrocoelium	D. lanceatum
Schistosomatoidea.	Schistosomatidae	Schistosoma	S. haematobium
			S. japonicum
			S. mansoni
			S. intercalatum

Class Cestoda

Superfamily	Family	Genus	Species
Bothriocephaloidea.	Diphyllobothriidae	Diphyllobothrium	D. latum
		Diplogonoporus	D. grandis
Taenioidea.	Davaineidae	Davainea	D. madagascariensis
	Dipylidiidae	Dipylidium	D. caninum
	Hymenolepididae	Hymenolepis	H. diminuta
			H. nana
	Taeniidae	Echinococcus	E. granulosus
		Taenia	T. solium
			T. saginata
	Anoplocephalidae	Bertiella	B. studeri

Note.—Two larval Taeniidae are found in man (Cysticercus cellulosae and Echinococcus granulosus); also two larval Diphyllobothriidae (Sparganum mansoni and Sparganum proliferum).

Life Cycle.—In the process of development from ovum to adult fluke, the organism passes usually through four larval stages. However, there are only 3 in the SCHISTOSOMATOIDEA. The ova are laid in the lumina of the hosts' organs or in the tissues, where the adult worms live, and directly or indirectly they reach the exterior. In the case of *Fasciola*, *Fasciolopsis*, *Clonorchis*, *Heterophyes*, *Schistosoma mansoni* and *Schistosoma japonicum*, this is accomplished via the faeces, while *Schistosoma hematobium* is usually eliminated in the urine, and *Paragonimus* in the sputum. The eggs passed in the faeces are composite; i.e., the ovum proper is surrounded by yolk cells necessary for its nutrition during development. In some species, segmentation is well advanced when the eggs are passed. In others it does not begin until the eggs reach water, and then, if the temperature is favorable and oxygen abundant, segmentation occurs. This results after 3 to 6 weeks in the development of the fully embryonated egg, which encloses the first stage larva or miracidium. The miracidium is a minute, ovoid, ciliated embryo without an alimentary canal and with only a primitive body space, but

provided with eye spots, excretory "flame cells," and secretory cells, or, e.g., in the sheep liver fluke, with a solid organ, the proboscis, at its anterior extremity. It escapes from the shell either by rupturing it or by forcing open the operculum.

The eggs of *Schistosoma* hatch soon after the excreta are diluted with water, but in the case of *Opisthorchis* and *Heterophyes*, only after ingestion by an appropriate molluscan host.

In the case of *Schistosoma*, *Fasciola*, *Fasciolopsis*, and *Paragonimus*, the miracidium assumes for a short time a free swimming existence, but is unable to take nourishment. Within about 24 hours, it either finds an appropriate gastropod molluscan host (a snail) or perishes. The mollusc thus constitutes the first intermediate host. In the case of *Opisthorchis* and *Heterophyes*, the ova hatch only in the oesophagus of the appropriate snail after they have been ingested in the egg stage. If the appropriate mollusc is present in the vicinity of the free miracidium, it is attracted by the fluid discharged by the mollusc and attacks the tentacles of the snail; by means of a lytic substance formed by the secretory cells it penetrates into the soft tissues, and makes its way to the lymph spaces around the digestive glands at the inner tip of the shell. It then loses its ciliated epithelium and in the course of a few days becomes greatly modified, becoming a simple, elongated, sacculated form without mouth or other distinguishable external or internal structures. It is now called a first generation sporocyst. The latter enlarges and the cells in the sporocyst wall proliferate to form many discrete masses which develop into rediae, the third larval stage. The rediae are eventually liberated by rupture of the sporocyst and make their way into the liver of the snail, where they undergo further development. The young rediae are minute, but they may attain a length of 2 mm. in the case of the liver fluke. They are also elongated, sac-like structures, but are characterized by possessing a simple blind alimentary canal and a collar-like constriction near the anterior extremity. Within the body of the rediae for a time a second generation of young rediae may develop and escape through a birth pore behind the collar. Eventually there develop within the body of the rediae numerous *cercariae*, the fourth larval stage. These are minute worms resembling the adults in having a leaf-like body provided with two suckers, and a bifurcated intestinal canal shaped like a two-tined fork. They differ in having a long slender tail which in the SCHISTOSOMATOIDEA is forked. The visceral mass of the snail in the course of a few weeks becomes densely packed with these larvae which are continually discharged throughout the life of the snail. Faust (1934), working with *S. mansoni* in Puerto Rico, found that a snail infected with a single miracidium might liberate 100,000 to 250,000 cercariae.

The cercariae leave the mollusc and swim about in the water. In the case of the liver fluke they lose their tails, crawl up blades of grass, and become encysted or encyst on the water. Here they remain until the grass is eaten or the water is drunk by a sheep or other suitable definitive host. In the case of the schistosomes the free-living cercariae penetrate the unbroken skin or buccal mucous membranes and after a migration through the blood stream come to rest in the portal system, where the parasites reach maturity.

However, the majority of the hermaphroditic trematodes make use of a second intermediate host, in which they encyst. Thus *Fasciola* encysts on vegetation in aquatic situations; *Echinostoma* encysts in a second molluscan host; *Clonorchis*, *Opisthorchis*, and *Heterophyes* encyst in the tissues of fresh or salt water fishes, while *Paragonimus* encysts in the soft tissues of crabs and crayfishes. No multiplication of the parasite occurs in this host, which serves mainly to protect and transport the parasite. The cercariae, after entering such a host, lose their tails, penetrate into the tissues, and encyst, but they may undergo further growth and development, into metacercariae as in *Paragonimus*. The parasite then lies dormant until the host is eaten by a suitable definitive host. Consumption of these second intermediate hosts, either raw or inadequately cooked, offers a means of infection for a definitive host, as man.

Whether the multiplicative process of the trematode within the mollusc is asexual or bisexual is disputed (Stunkard, 1936).

Mollusc Hosts.—In those trematode infections of man of which we know the life history, some species of mollusc serves as an intermediate host. The phylum *Mollusca* includes unsegmented animals, usually

contained in a calcareous shell and made up of visceral mass, head, mantle and foot. The mollusc hosts of trematodes belong to the class Gastropoda, which are known as snails, and usually have a spirally coiled shell, a distinct head and a broad flat foot. The molluscs concerned in transmitting flukes have a foot flattened ventrally and are creeping forms (Platypoda). Gastropods with a fin-shaped foot are free swimming forms (Heteropoda).

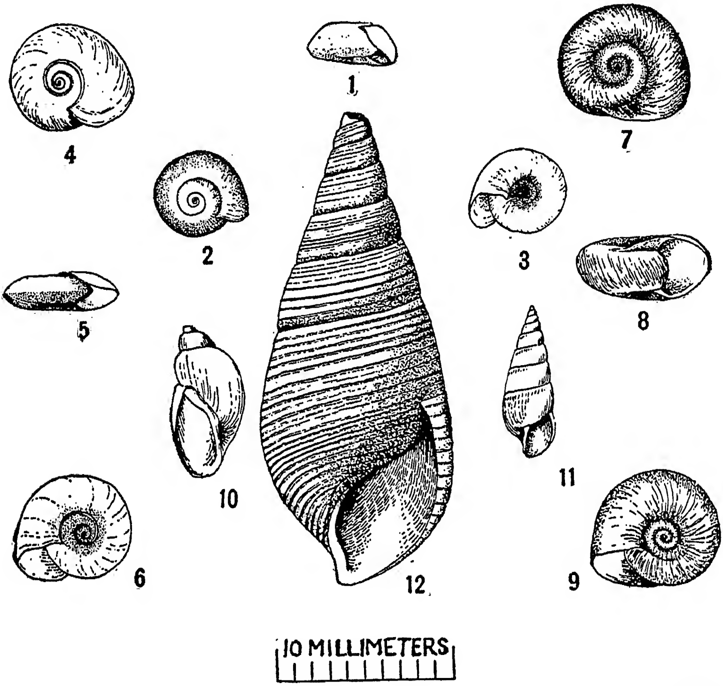

FIG. 331.—Mollusc hosts of human trematodes. 1–3, *Segmentina;* 4–6, *Hippeutis;* 7–9, *Planorbis boissyi* Potiez and Michaud; 10, *Bulinus contortus;* 11, *Katayama nosophora* Robson; 12, *Melania libertina* Gould. (By Courtesy of Paul Bartsch.)

The following are the more important flukes of man with some of the genera of mollusc hosts which have been demonstrated or suspected.

There is still much difference of opinion and confusion as to the nomenclature of these snails. *F. hepatica—Lymnaea truncatula; F. buski—Segmentina* and *Planorbis (Hippeutis); Paragonimus—Melania* (and *Pomatiopsis* in Michigan); *O. felineus—Dreissena; C. sinensis—Bythinia* and *Parafossarulus; M. yokogawai—Melania; D. lanceatum—Zebrina; S. haematobium—Bulinus* (chiefly), *Physopsis, Lymnaea, Planorbis pfeifferi; S. mansoni—Planorbis* (chiefly), *Physopsis, Bulinus; S. japonicum—Oncomelania, Katayama (Blanfordia)* and *Schistosomophora.*

Lymnaea, host of *F. hepatica,* is a common snail of ponds. It has a delicate fragile elongated shell with a pointed spire and a dextral opening.

Melania, the host of *Paragonimus,* an operculated aquatic snail, has a turreted shell with an acute apex.

Planorbis, the principal host of *S. mansoni,* also aquatic, has a rather thick shell rolled in a flat spiral. The spire of the shell is in one plane. The shells of *Segmentina* (the host of *F. buski*), and of *Hippeutis* have a similar shape.

Bulinus, the principal host of *S. haematobium*, has a short spire with a pointed apex and a sinistral opening. It is found in canals and ponds. The shell of *Physopsis* is similar.

Oncomelania (with ribbed shells) and *Katayama* (or *Blanfordia*) (with smooth shells), the hosts of *S. japonicum*, have slender tapering shells 5 to 12 mm. long, with many whorls and a pointed apex. There is a coarse ridge on the external surface of the sharp outer lip. They are amphibious and operculated.

Experimental infection of snails by miracidia show that these tend to avoid unsuitable hosts and attack only certain hosts. Many miracidia, however, attack snails which are not efficient hosts and undergo partial development. Various species of a genus (but not all) may act as hosts. Mollusc hosts are not so restricted in their range of parasites or the flukes so restricted in their range of hosts as they were formerly thought to be.

Schistosomiasis Produced by the Human Schistosomes or Blood Flukes

The most important of the flukes which are parasitic in man are those which are found in the blood vessels. Such infections are exceedingly common in Egypt and in certain areas in the Orient, and occur in many parts of tropical Africa and South America. The disease is commonly called schistosomiasis, since the human parasites all belong to a common genus, *Schistosoma* Weinman (1858).

Morphology.—The schistosomes differ from other flukes in many respects. They are dioecious (sexes separate), instead of hermaphroditic. There is no pharynx. The gut-branches reunite to form a single caecum. The eggs do not have an operculum. In the larval stages asexual multiplication occurs only in the sporocyst stage, no rediae being formed. The cercariae have forked tails, but no pharynx. They penetrate the unbroken skin or mucous membranes by means of a lytic substance secreted by the single-celled cephalic glands, and do not require a second intermediate host.

The males are from about 10 mm. to 20 mm. long. The anterior fifth of the body is cylindrical, but the posterior four-fifths is flattened and thin. The margins, however, are infolded ventrally to form the gynaecophoric canal in which the female is enclosed during copulation or after sexual maturity is reached. The small testes are grouped just behind the ventral sucker. The female is about 20 to 26 mm. long, filariform, and darker in color than the male. Both extremities project from the canal of the male, in which she lives. The ovary lies anterior to the union of the gut branches.

Life History.—The flukes live in the portal vein and its branches. From the study of human infections and the more recent observations of Fairley on living monkeys infected with *S. haematobium*, the paired worms travel against the blood stream into the finer branches of the mesenteric or pelvic veins. The female leaves the male and penetrates as far as possible into the venules, greatly distending them. As she withdraws she deposits the ova, one at a time, with the spine pointing backwards. The elastic veins contract down about the ova, and the force of the blood stream tends to force the spine through the vessel wall. The ova cause a local inflammatory reaction and finally ulceration, so that many of them reach the lumen of the bladder or rectum, and then are passed in the urine or faeces. The eggs contain a developed miracidium when passed. On reaching water the shell quickly ruptures, probably as a result of high osmotic pressure in the egg. The miracidium escapes and seeks a suitable intermediate host a species of snail. The eggs die in a few days in undiluted faeces or urine. As compared with other flukes, schistosomes produce relatively few eggs.

Infection is usually acquired by wading or bathing in infected water into which the cercariae of the *Schistosome* have been discharged from the infected snails. The cercariae come in contact with the skin and as the water evaporates they enter the skin for protection, casting off their tails. Penetration of the skin of man by the cercariae may give rise to an intense pruritus and erythema, called in Japan "kabure," or in Puerto Rico, "piquina." The parasites (0.100 to 0.200 mm. long) burrow into a vessel, are carried by the blood stream to the lungs, and make their way to the liver

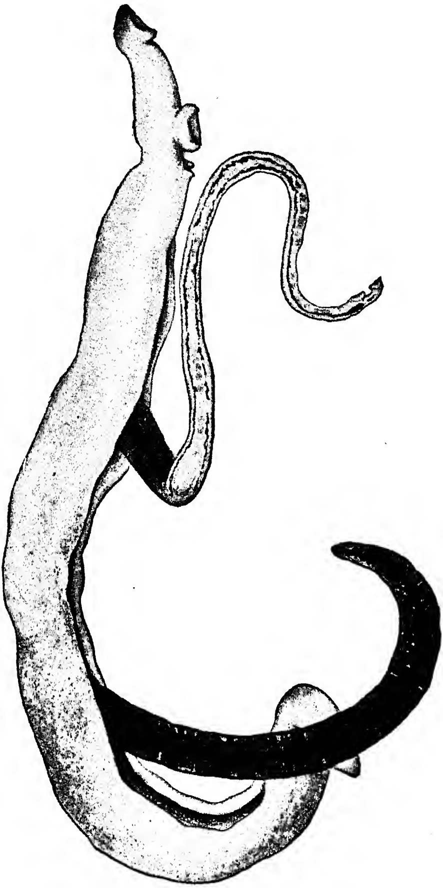

FIG. 332.—*Schistosoma japonicum* (male and female). The sharp edges of the borders at the beginning of the gynaecophoric canal formed by the male are an accidental appearance. (From Mense.)

and portal veins. About a month after the parasites enter the body there is often a period of fever, associated with urticarial eruptions, frequently cough, abdominal pain, and a leukocytosis with a marked eosinophilia.

The period required for the development of the characteristic *local lesions* about the ova varies from 6 to 8 weeks to 2 years or more. These lesions are dependent on the reaction of the tissues to the irritation caused by the eggs of the parasites. They differ in detail with the species of parasite concerned. They involve primarily the wall of the bladder or colon, in which most of the eggs may be deposited. Many eggs, however, are washed out of the veins in which they were deposited and carried by

the portal vein to the liver, and in smaller numbers to other organs, including the kidneys, lungs and brain. In such locations, particularly, the damage is manifestly cumulative, and not rarely leads eventually to a fatal portal cirrhosis. As suitable treatment with antimony, may kill the adult parasites and destroy the ova, it is evident that early diagnosis is of importance to the patient.

Three species are of great pathogenic importance in man: *Schistosoma haematobium*, which causes vesicular schistosomiasis; *Schistosoma mansoni*, which causes intestinal schistosomiasis and Egyptian splenomegaly; and *Schistosoma japonicum*, which causes intestinal and hepatic schistosomiasis. However, at least 3 other species have been reported as rare or potential human parasites.

I. Genito-urinary Schistosomiasis Due to Schistosoma Haematobium

Synonyms.—Bilharzia disease, bilharziasis, endemic haematuria.

Definition.—A chronic disease due to invasion by the parasite *Schistosoma haematobium* of the pelvic veins, particularly the vesiculo-prostatic

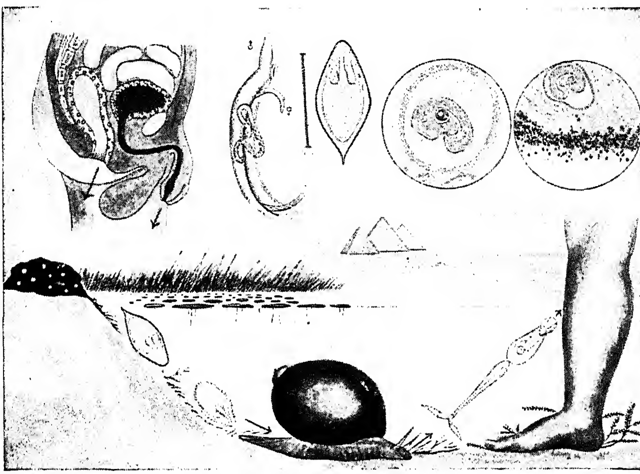

FIG. 333.—Method of infection in schistosomiasis. (After Fülleborn.) For explanation of details, see in addition Fig. 334.

and the pubic and uterine plexuses. The ova of the parasite, which become deposited in the mucous membrane of the bladder and are frequently passed in the urine, give rise to haematuria, cystitis, urinary calculi, and other genito-urinary disturbances. When the ova are deposited in the walls of the rectum, mucosanguinous discharges may result, which also contain ova.

History.—The Egyptians have undoubtedly suffered from this disease since very ancient times, and the history of it in that country extends over thousands of years. Ruffer (1910), in the histological study of certain mummies of the 20th dynasty (1250–1000 B.C.), found in the kidneys bilharzia ova situated for the most part among the straight tubules.

This observation was confirmed by Looss, and the writer shortly afterwards had the opportunity to obtain and study such histological material in Egypt. It is interesting in this connection that the papyrus Ebers contained a prescription which has been thought to have been for the treatment of one of the most prominent symptoms of infection with bilharzia, namely haematuria. Sandwith, in his *Medical Diseases in Egypt* (1905) states that in Napoleon's campaigns in Egypt (1799–1801) the French troops suffered severely from haematuria.

The parasite responsible for the disease was discovered by Bilharz (1851) in the mesenteric veins of a native of Cairo and he shortly after demonstrated the parasite to be the cause of haematuria in the natives who were discharging the terminal spined eggs produced by the parasite in their urine. Cobbold named the parasite in honor of its discoverer, *Bilharzia*, creating the generic name. However the name *Schistosoma* had been applied by Weinland 3 months earlier, in 1858, and thus had scientific priority. Nevertheless, the term Bilharzia has been employed for many years in Egypt and, indeed, is still the popular term applied to both the parasite and the disease in that country. Manson-Bahr (1940) still retains it and alludes to the genus *Bilharzia* (Meckel, 1856).

Although Harley, who found the parasite in South Africa in 1864, and also Cobbold, believed some mollusc served as the intermediate host and that the portal of entry for the infective stage was probably the skin, Looss, who studied the question from 1894 to 1914 failed to discover the life cycle and concluded that there was no intramolluscan cycle.

The discovery of lateral spined eggs, usually in the faeces, in contrast to the terminal spined ones encountered in the urine, suggested to Manson, 1893, that there might be 2 species of human *Schistosomes* in Egypt, and Sambon (1907) designated the hypothetical species with lateral spined eggs as *Schistosoma mansoni*. However, definite proof of the existence of 2 separate species was not given until Leiper, 1915–18, from further studies of the life history, showed that there were 2 distinct species, one typically intestinal with lateral spined eggs and one typically vesicular with terminal spined eggs, that these species were morphologically distinguishable, and that they required a different molluscan intermediate host.

Miyagawa, Miyairi and Suzuki had previously (1913–14) demonstrated in the allied infection produced by *Schistosoma japonicum* the complete life cycle of that parasite, describing the intramolluscan stage and showing that infection was acquired by the cutaneous route. This work, which was studied by Leiper in Japan, provided a basis for his later work on the blood flukes in Egypt.

McDonough, in 1918, advocated the use of tartar emetic as a specific in the treatment of vesicular schistosomiasis and the value of this drug on a large scale was demonstrated by Christopherson in the same year.

Geographic Distribution.—The disease produced by *Schistosoma haematobium* has a wide distribution in Africa, including the Sudan, Ethiopia Uganda, the Congo and Rhodesia. It is common throughout the Union, of South Africa, especially in Natal. It is also found in West Africa, especially Liberia, and Sierra Leone. In North Africa it is common in Morocco, Algeria, Tunis and Egypt. Along the East Coast it extends from Ethiopia to the Cape.

It also occurs in western Asia, Arabia, parts of Palestine, Iran, Iraq, and in the lower edge of Portugal, near Tabiera, in Greece in the Island of Cyprus, and it is also found in the islands of the east coast of Africa, Madagascar, Mauritius and Reunion. A few indigenous cases were reported over 30 years ago from western Australia (Manson-Bahr,

1940). Two cases were also reported from Australia following the return of infected troops from Egypt after the World War. However there is no evidence that *S. haematobium* infection has ever been endemic in the western hemisphere. Several cases were reported in the United States some years ago. Faust believes that these were undoubt-

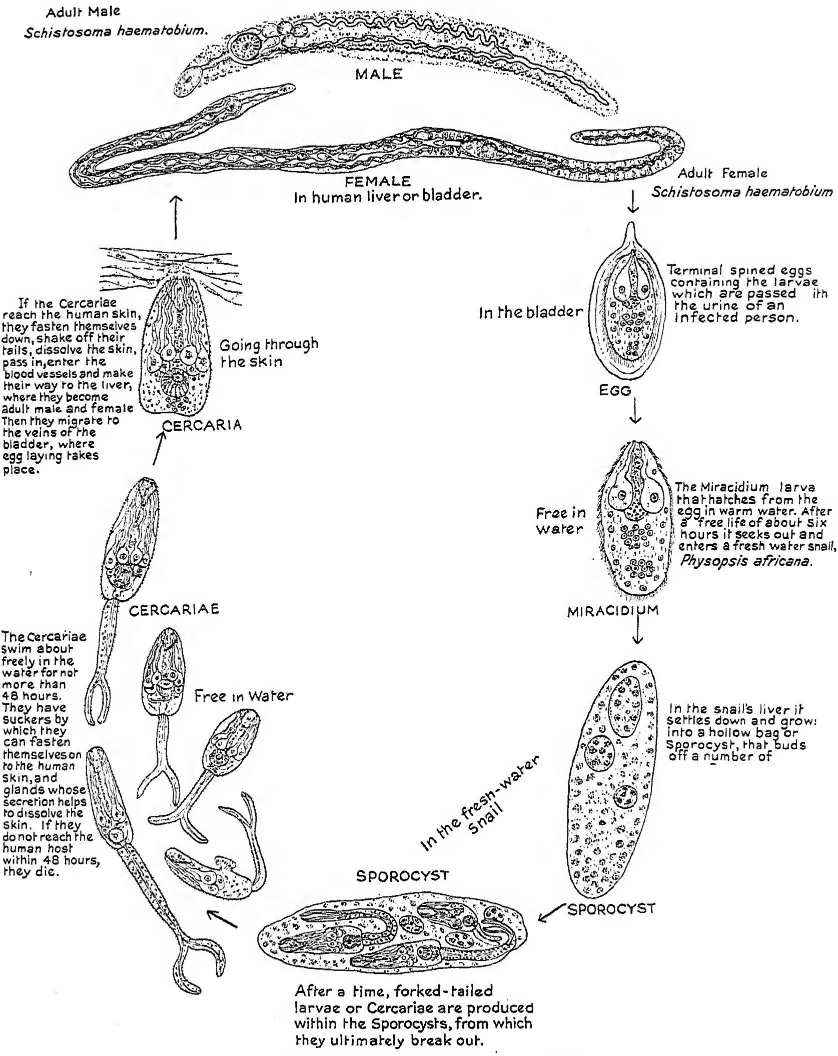

FIG. 334.—Life cycle of a human *Schistosome*, as exemplified by *Schistosoma haematobium*. (After Dr. Annie Porter. Courtesy South African Institute for Medical Research.)

edly examples of spurious parasitism. On the other hand, *S. mansoni* is very prevalent in parts of Central and South America.

Prevalence.—In some countries schistosomiasis causes more sickness and death than any other single disease. Scott (1939) estimates that

at least six million of the twelve million rural inhabitants of Egypt are infested with *S. haematobium* and three million with *S. mansoni*. At least one and a half million are infested with both species together, and about seven million with schistosomiasis of either one or both species.

The distribution in Egypt varies, and for the purposes of study the country has been divided into 4 regions. In three, about 60 per cent of the rural population was found to be infested with *S. haematobium*. In the first of these, in the north and eastern parts of the delta, about 60 per cent were also infected with *S. mansoni*, while about 85 per cent showed either one or both species. In the second region, in the southern part of the delta, *S. mansoni* infested not more than 6 per cent, although the transmitting

FIG. 335.—Transverse sections of *S. haematobium* lying in vessels in sections of papilloma of the bladder, with a few calcified ova in the subserus connective tissue.

snails seemed to be as abundant as in the first region. No topographic, hydrographic or demographic differences between these regions could be noticed, although the line of demarcation was very sharp as far as prevalence of the parasite was observed. In the third and fourth regions, in the Valley of the Nile and to the south of Cairo, the snail hosts of *S. mansoni* have never been found. In the third region then, *S. haematobium* was found alone and infested 60 per cent of the population. In the fourth region, *S. haematobium* was found in less than 5 per cent of the people. In districts where 5 per cent of the inhabitants are infected, one in a thousand die from the infection. However, in the first named districts the proportion rises one to twenty-two.

In many other parts of Africa and in tropical America, at least in local areas, schistosomiasis must be ranked among the very dangerous human

diseases and in vast areas in China *Schistosoma japonicum* is also an important human scourge. Scott (1940), in the lower valleys of Venezuela, found that the percentage of infection with *S. mansoni* was for males about 80 and for females about 60 per cent. In the males above 10 years it reached 90 per cent.

Snails were found infected in different localities from 10 to 75 per cent, and he believes that schistosomiasis in Venezuela is as severe as anywhere in the world.

Etiology.—In *Schistosoma haematobium*, the male is shorter, and stouter, than the female, measuring 10–15 mm. in length by 0.8–1.0 mm. in breadth. It has a finely tuberculated cuticle and 4 testes. It also has 2 muscular suckers, the ventral being larger.

Behind the ventral sucker, the body of the male is infolded ventrad with the caudal extremity forming a gynecophoric canal in which the female is enclosed, during copulation and oviposition. The female is long and slender, measuring about 20 × 0.25 mm. The suckers are small, subequal, and not conspicuously muscular. The ovary is in the posterior half of the body. The ova, after being fertilized, are passed into the uterus, which contains 20–30 eggs at one time. The eggs measure from 112 to 170μ by 40 to 70μ They have a yellowish brown, transparent shell and a distinct terminal spine. The eggs are deposited chiefly in the veins of the bladder and occasionally a few in the rectum. They are commonly discharged in the urine, usually at the end of micturition but occasionally they are passed from the rectum. On dilution of the urine with 10 or more parts of water, viable eggs soon hatch and the miracidia escape as free-swimming organisms, which may infect the snail serving as the intermediate host.

The following snails have been reported to serve as effective intermediate hosts: *Bulinus truncatus* (Egypt, Cyrenaica and Tunis); *B. forskali* (Mauritius, and possibly Kenya Colony); *B. tropicus* (South Africa); *Physopsis africana* (South Africa and the Belgian Congo; *P. globosa* (Sierra Leone, West African Coast, northern Nigeria, Nyasaland, and Rhodesia); *P. nasuta* (Kenya Colony); *Planorbis dufourii* (Portugal and Morocco).

On leaving the snail, the cercariae swim about in the water, at times sinking to the bottom and then again swimming back to the surface where they may become attached for a period by their ventral suckers. When human beings bathe or wade in such water, the cercariae come in contact with the skin and as the water evaporates they enter the skin for protection, casting off their tails.

The period of their free living existence is short being limited at most to 3 days, usually to 24 hours or less. Entry through the outer portion of the epidermis takes place in less than half an hour and usually within 20 to 24 hours the larvae or metacercariae have gained access to the peripheral venules.

Pathology

The earliest manifestations of the disease are associated with the entry of the larvae into the skin, which may result in intense pruritis, depending on the intensity of the exposure and the sensitiveness of the individual. Some minute petechiae may be seen at the sites of the invasion of the cercariae into the blood vessels. Some days later there may be an urticarial rash. Sometimes, still later, in severe infections, toxic symptoms consisting of anorexia, headache, generalized pain in the

back and extremities, and a rise of temperature accompanied by a rigor and night sweats occur. The blood often shows a leucocytosis, and eosinophilia is sometimes as high as 50 per cent. In some instances the abdomen becomes swollen and tender, the liver and spleen enlarged, and there may be precordial pain. Usually there is no diarrhoea or dysentery, unless some of the ova have invaded the rectum.

Several months may intervene between the deposition of the eggs in the tissues and their first appearance in the urine. Eventually there is apt to be an increasingly frequent burning at the time of urination and an increased desire to urinate. Cystoscopic examination may reveal hyperplasia and inflammation of the mucous membranes of the urethra and lower segment of the bladder. Papillomatous growths may also be observed in the lumen of the bladder. Such pathological changes are particularly due to the deposit of the ova in the tissues.

Their presence gives rise to a round cell infiltration, the proliferation of the epithelial cells and the production of what has been called bilharzial granulation tissue, which at first assumes a hypertrophic and later an atrophic form. In the hypertrophic form, which is more common in the mucous membranes, there is marked proliferation of the epithelium which leads directly to the formation of papillomatous growths or to the formation of vesicles containing turbid fluid. By bursting, these may give rise to ulcerations. In the atrophic form, the granulomatous tissue becomes more fibrous as the process becomes less acute and in these areas very few ova may remain. In sections, the ova may be seen escaping between the epithelial cells of the mucous membrane. The fine capillaries and veins beneath the epithelial lining and the loose connective tissue in which they occur are also often filled with ova, while in the deeper subcutaneous tissues coupled pairs of the worms are often found in the vessels. The amount of round cell infiltration and of fibrous tissue present varies according to the age of the process.

One of the earliest manifestations of schistosomiasis in the mucous membranes is a characteristic velvety swelling. The surface is usually dark red and has the appearance of a thick velvet. In other instances in the mucous membrane of the bladder there may be a fine brownish-yellow, powdery appearance, with here and there the development of sandy patches in the wall. In the small papillomatous outgrowths, the central core is vascular and composed of loose connective tissue, being practically continuous with the submucous tissue. The core of the papillomata is infiltrated with leucocytes, lymphocytes and eosinophiles. Later giant cells make their appearance. The ova are scattered irregularly throughout. As the ova approach the surface of the mucous membrane in large numbers, the surface epithelium undergoes necrosis, the papillomata become granular and shiny and bleed easily. These also frequently ulcerate, particularly when they occur in the intestine. The ulcerations may also occur in the intestine independently of the formation of papillomata and deeply punched out like ulcers may result and give rise to symptoms of dysentery. At a later stage in the bladder, the whole mucous membrane may be so altered in color and structure that a regular calcified lining is formed, which gives at autopsy a characteristic gritty feeling to the hand. The walls of the affected organ in these instances are generally large and thickened, partly from muscular hypertrophy and partly from the deposit of fibrous tissue. In the bladder, the eggs not only give rise to haematuria but constitute the nucleus for calculi. Cystitis results usually, and frequently extends to the ureters of the kidneys. Dila-

tation of the ureter and of the pelvis of the kidney frequently results from prevention of the outflow of the urine, either due to lesions of the bladder or in the ureters themselves. Lesions of the urethra may lead to fibroid thickenings and fistula in the male. In women, the vagina, vulva and cervix are particularly involved. Large areas of the adjacent skin may become riddled with discharged sinuses, the track of which is lined with granulation tissue in which the ova are found.

FIG. 336.—Section of wall of bladder showing ova of *Schistosoma haematobium*, some of which have undergone calcification.

SYMPTOMS

The symptoms of infection with *Schistosoma haematobium* are very variable. In many cases the infection is practically symptomless, but in other instances the suffering is very great and the infection ultimately results in death. Early toxic symptoms, such as fever and urticaria, may come on within a month after exposure to infection. On the other hand, the incubation period from the time of infection to development of symptoms of definite organic disease may vary from 3 months to more than 2 years.

The most striking symptom indicating deposition of the ova in the mucous membranes of the bladder is passage of blood at the end of micturition. Generally it is only the last few drops of urine that contain blood, but in severe cases the haemorrhage is more extensive and the urine may be blood tinged throughout. Occasional clots are present. In such urine one almost invariably finds large numbers of terminal spined eggs. Sometimes when they are not discovered in a large sample of

urine one can find them in the last few drops passed, especially in the urine which is forced out by straining. Pain is not always present, but in other instances there may be pain in the suprapubic region or in the perineum. Frequency of micturition is often an early common symptom and there may be a scalding sensation of the urethra during and after passage.

The endemic haematuria may last for months or years and when the infection is severe, cystitis soon supervenes and may give rise to considerable suffering. In chronic cases the eggs not infrequently become the nucleus for the formation of calculi and large stones are not uncommon, especially in Egypt. Multiple small stones are also encountered.

Papillomata which develop in the walls of the bladder not infrequently become malignant. Brumpt, 1936, has made a careful study of the role that *Schistosoma* plays in the production of human carcinoma.

A statistical study made in Cairo showed that the association of schistosomiasis and of carcinoma of the bladder is from 2 to 11 times more frequent than "pure" cancer of the bladder. Sorour in a study of 413 cases of schistosomiasis of the bladder, of which 393 were in men and 20 in women, found that among the 393 men there were 78 cases of carcinoma of the bladder, 3 of bilharzial endothelioma of the perineum, 4 of bilharzial carcinoma of the rectum, 1 of bilharzial carcinoma of the caecum, and 1 of bilharzial epithelioma of the skin in the inguinal region. His statistics further show that bilharzial carcinoma of the bladder appears in the first period of life, 15–20 years of age, and that it becomes augmented in frequency as age progresses.

Besides symptoms of the bladder, there may be evidences of prostatic disease or of vesiculae seminales involvement. In the latter case ova may be detected in the semen. In other instances, symptoms develop in connection with lesions of the ureters and kidneys. Dilatation of the ureters and hydronephrosis may take place and attacks of renal colic may occur in such instances, secondary septic infection of the urinary tract is frequently a complication. Many of the patients become anaemic, wasted and debilitated. Urinary fistulae are not uncommon in connection with disease of the urethra. They are especially common in the perineum and posterior surface of the scrotum. Stricture of the urethra is by no means uncommon.

Pseudo-elephantiasis of the sheath of the penis may also occur, in which ova are found deep in the tissues. Infection of the spermatic cord is not infrequent. In women, vaginitis and cervicitis may occur and papillary growths and ulcers, which may in some instances become malignant. Papillomatous masses containing ova are also sometimes found on the vulva and may simulate venereal warts. Surour found in 20 women infected with schistosomiasis there were 2 cases of carcinoma of the bladder.

Rectal symptoms, with passage of blood and mucus, may coexist with urinary symptoms. These lesions may be due to invasion of the intestinal wall with *S. haematobium*, or to mixed infections, with *S. mansoni*. Both Khalil and Scott have pointed out that a high percentage of the people in parts of Egypt are infected with either one or both species.

Rarer Lesions.—It seems not improbable that almost any organ of the body may sometimes be invaded by *Schistosoma hematobium*.

Thus the ova may be carried into the inferior mesentery veins and give rise to *Schistosoma* appendicitis. Campbell, in northern Nigeria, found ova in 57 per cent of the appendices removed by operation. He considers that the infection may produce symptoms requiring urgent surgical

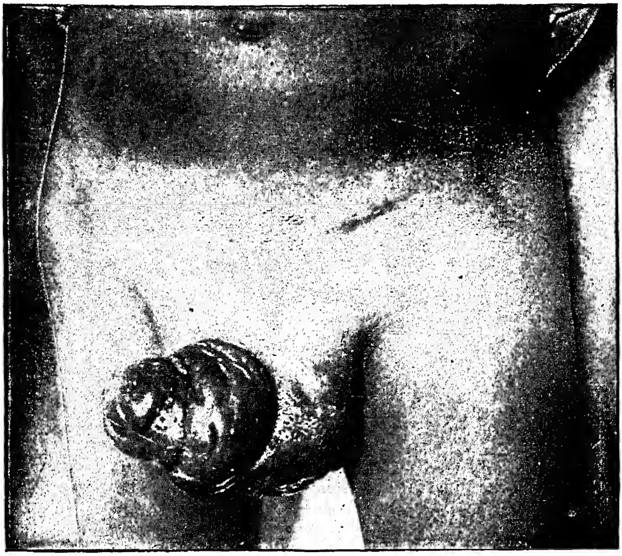

FIG. 337.—Vesical schistosomiasis showing fistulous tracts opening from penis and scrotum. (From Ruge and zur Verth.)

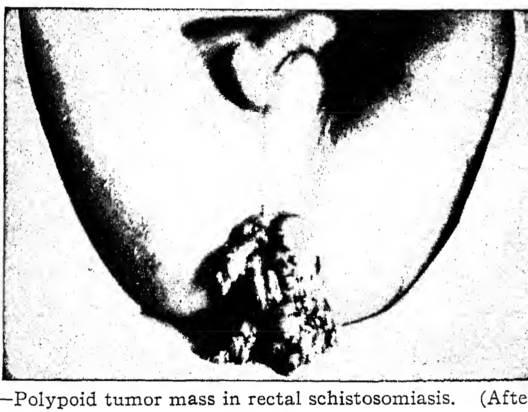

FIG. 338.—Polypoid tumor mass in rectal schistosomiasis. (After Madden.)

intervention. Sargent (1937) and Kaufmann (1937) have also called attention to *Schistosoma* appendicitis. Usually, however, the presence of the ova in the appendix does not result in *acute* inflamatory attacks.

Small numbers of ova are also frequently swept back through the portal vessels into the liver, where pseudotubercle formations and sometimes abscesses result, followed by polypoid fibrosis of the periportal tissues. Makar has reported primary disease of the gall bladder giving

rise to duodenal stasis. The interior of the bladder was studded with sandy patches such as are more frequently seen in the urinary bladder.

The ova, and even the parasites, may be carried through the hypogastric and common iliac veins and inferior vena cava and the right heart and then become located in the lungs. Turner has pointed out that large numbers of the ova in the lungs may give rise to a form of interstitial pneumonia. Suarez (1931) has reported an infection of the lungs may give rise to symptoms simulating bronchial asthma. Shaw and Ghareeb (1938) have found pulmonary lesions due to the ova of *Schistosomes* in 33 per cent of 282 autopsies upon Egyptians. *S. haematobium* was almost twice as common as *S. mansoni.*

Adult worms were found in 10 per cent of the pulmonary cases. Ova reached the lungs as emboli and caused an acute necrotising arteriolitis. The ovum escaped through the vessel wall and became the center of a parenchymatous tubercle. In some instances they found an increased intrapulmonary blood pressure with diffuse arterial changes and hypertrophied right ventricle producing a condition resembling Ayerza's disease.

Ova have also been found in the brain and spinal cord in patients who have suffered with epileptic and paralytic symptoms.

Day and Kenaway and Bayoumi (1939) each have reported cases of bilharzial myelitis, the ova being demonstrated at autopsy in the lumbar enlargements of the cord. In Bayoumi's case, there were sandy patches in the bladder and the whole length of the ureters and in the seminal vesicles, where ova were also found. Hoffman and Shady, (1939) have reported 4 cases, one with myelitis and all with mental confusion, in which the nervous and mental symptoms were relieved after treatment with tartar emetic. Gazayerli (1939) found schistosome ova in the circumflex branch of the left coronary artery of a patient in Egypt who had died of meningitis. Lesions were also present in the lungs, rectum, appendix and urinary organs, and the ova of *S. hematobium* were found in the scrapings.

In rare instances the adult worms themselves, in copula, have sometimes been found in the urine in connection with a copious hemorrhage with ruptured vessels.

Diagnosis.—Diagnosis depends upon finding the ova with a terminal spine in the urine. More rarely, they may be found in the faeces, Fig. 339.

A *complement fixation* test has been devised by Fairley (1917), with an alcoholic extract of the livers of snails infected with *S. mansoni* as antigen. He obtained positive reactions in a large proportion of cases of early infection with both *S. mansoni* and *S. haematobium,* and believes it can be used to check the results of treatment. The method promises to be of practical value, if a standardized antigen can be made available.

Fairley obtained positive *cutaneous reactions* (also group reactions) by using filtered saline extracts of infected livers. These reactions persisted after apparent cure.

The presence of haematuria in areas where the disease is endemic is a suggestive symptom in diagnosis. Cystoscopic examination and sometimes digital examination will often give suggestive information. The disease should be distinguished clinically, especially from renal calculus due to other causes and from benign and malignant growths of the bladder and rectum and from haemoglobinuria and bacterial cystitis.

Prognosis

In the milder degrees of infection which are the commonest, the patient is usually not inconvenienced by the parasite, though in almost all cases there may be attacks of haematuria from time to time. In severe chronic infections, however, much suffering usually results and as a consequence anaemia and debility follow. The intensity of the infection is important in connection with the prognosis. In severe cases, chronic cystitis is very common, and calculus may result, or grave renal disease follows. The papillomatous or epitheliomatous outgrowths in the bladder may become malignant. In recent years the discovery of the value of antimony in the treatment has greatly improved the prognosis in the majority of cases in which it is instituted early.

Prophylaxis

Especially in urine and faeces of infected individuals which contain the ova lies the source of the polution of water in which the snails which constitute the intermediate host become infected. Hence it is most important that there should be disinfection or other sanitary disposal of excreta and every attempt made to prevent the evacuation of infected excreta into the surrounding water supply.

In the endemic districts, man frequently acquires schistosomiasis from bathing, wading, and washing in streams and pools where *Schistosoma* cercariae are present. Infection may also result from drinking such infected water.

Therefore prophylactic measures also should be directed toward education of the population to refrain from drinking from, or bathing in, the rivers, ponds and canals, and sportsmen should be warned against wading in localities known to be infected. In such localities, drinking water should also be boiled. The cercariae can usually live free only 24 to 48 hours in water. Hence impounding infected water makes it safe for bathing and drinking, as does also its superchlorination for more immediate use.

Other important means of prevention are chemotherapeusis of infected individuals and antimolluscan campaigns.

As regards sterilization of drinking water, boiling is by far the most satisfactory method. Chlorine in the strength of 1:1,000,000, which has generally been employed to sterilize drinking water, appears to be ineffective upon the living cercariae. However, Witenberg and Yofe (1938) have reported that gaseous chlorine is really the only agent which can be employed practically and that can be depended upon to kill the cercariae.

Chlorine water containing 2 grams per liter is prepared by introducing gaseous chlorine directly into the water. Two grams of ammonium chloride (NH_4Cl) are then dissolved in 100 cc. of this chlorine water. The solution is then left to stand for 2 hours at room temperature. Of this solution, 2.5 cc. are dissolved in 1 liter of water. This forms a stock chloramine solution which contains from 1 to 2 parts per million of active chloramine. They found chloramine to be the most effective form of chlorine tested. With chloramine, a lethal effect was certain in less than 30 minutes if 0.22 per million of

available chlorine remains after 10 minutes. Lower concentrations are not certain, even if longer periods are allowed. If sodium hypochlorite is used, a sure effect may be expected during 1 hour and 5 minutes, if there remains 0.28 per million of available chlorine, and during 30 minutes if 0.42 per million or more of available chlorine remains

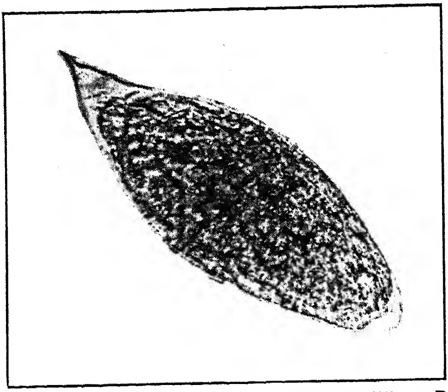

FIG. 339.—Ovum of *Schistosoma haemotobium.* (After William Pepper from Jefferys and Maxwell.)

FIG. 340.—Ovum of *Schistosoma mansoni.* (After William Pepper from Jefferys and Maxwell.)

after 10 minutes. If gaseous chlorine is used, a sure lethal effect will be obtained if the amount of the available chlorine after 10 minutes is 0.25 per million.

Sproule (1939) has also found after extensive experiments that chlorination will destroy cercariae, provided that the amount of chloramine employed equals that as indi-

cated as necessary by Horrock's water testing method plus 2, a contact period of half an hour being advised.

Brackett has reported that the cercariae are very susceptible to formaldehyde and that a 0.03 per cent solution will kill them in 1 minute or less.

For the destruction of snails, ammonium sulphate in weak solutions has been recommended, since it kills the snails in a few hours. Copper sulphate in high dilutions, 1:100,000 and sometimes even 1:1,000,000, will also kill the snails. Care should be exercised that the copper is not introduced in a strength that will kill the fish.

Brackett (1939) points out that in this connection copper carbonate, which is less soluble, can safely be applied in excess. He recommends 3/10,000 of a pound for each calculated cubic foot of water. However, the organic matter in the water may fix the copper and render it inert. In some localities, the pumping of live steam into the water has been the most satisfactory measure to kill the snails. The snails may withstand drying for considerable periods and some which burrow in the mud may survive.

A mollusc once infected may continue so for months, but fortunately the free cercariae live but a very short time, at most some 48 hours, in water. Free cercariae, however, readily pass through the ordinary municipal filter beds and they can traverse 30 inches of fine sand in 5 hours. In Egypt, in recent years the destruction of the snails in some localities has been attempted by adding a preparation called "Sizolin," 1:200,000, to the water. However, very great difficulty has attended the attempts in Egypt to eradicate the snails in endemic regions. Thus Khalil reported that in one region the *Bulinus* snails were completely exterminated in an isolated irrigated region by mixing copper sulphate, 1:200,000, in the entering water, but a few months later the Bulinus snails were present in large numbers, and it appears that parts of the Nile itself contain infected snails.

Scott and Barlow (1938) in reporting upon the sanitary campaigns carried out during a six year period in Egypt state that while a reduction in the amount of infection followed the administration of as much treatment as the people could be persuaded to take, and that such sanitary measures as were possible were carried out, nevertheless after two years the rate of Schistosoma infection had returned approximately to its original level. Thus the chemotherapeutic program was unsuccessful, especially due to constant reexposure, and the infection itself appeared to confer little if any immunity to subsequent infection.

Scott and Barlow, however, emphasize that the fact that sanitation did not cause, or even maintain, a lower level of parasite infection should not militate against its value and that it has, of course, relieved much suffering. They emphasize that complete elimination of urine and faeces from the canals would put schistosomiasis under control, since in Egypt there is no rain to wash polution into the water, and the entire difficulty is based on customs which lead to direct polution of the canals.

Control of the snail hosts could also reduce the level of infection. However, the simple drying of the canals was not found to be effective, as some of the snails burrow into the mud. Nor did the use of chemical agents appear to be practical. Keeping the canals free from vegetation appeared to be a satisfactory means of reducing the number of snails.

Cawston (1944) thinks that prophylaxis is particularly a problem for the engineer: forced disturbance of water containing the fragile cercariae being more serviceable than chemicals.

Apparently the only permanent advance in the control of the disease in such countries as Egypt and Venezuela will result when proper disposal of human excreta is secured.

Treatment

The intravenous injection of tartar emetic as employed for treatment of Schistosomiasis by McDonagh and Christopherson has proved of great value in the treatment of all forms of schistosomiasis. The drug

apparently acts upon the adult trematode by cumulative action. Under normal conditions, when the freshly passed urinary deposit is mixed with warm water at 130°F., the hatching of the eggs usually takes place in about 5 minutes, but after the patient has received injections of antimony tartrate it is found that such eggs as appear in the urine are dark and shrivelled and contain dead miracidia. Christopherson believes the change to be due to the direct action of antimony upon the eggs. Fairley, from experimental studies on the allied species, *S. spindalis*, of the goat, believes that antimony acts first in a selective manner upon the reproductive organs of the female bilharzia and thus causes first a shrunken appearance of the egg and second a cessation of egg laying capacity, finally a destruction of the adult parasites occurs.

Tartar Emetic. **(Sodium Antimony Tartrate).**—It is recommended that the intravenous injections be given on alternate days over a period of 4–6 weeks. It is usual to begin with ¼ grain (0.015 Gm.) doses for children; and ½ grain (0.03 Gm.) for adults dissolved in 20 minims of distilled water and then diluted with an equal amount of normal saline. The dose is increased by ½ grain until 2½ grains (0.16 Gm.) is reached, unless a reaction is produced before that time. Injections are then given every other day, the dosage being kept between 2 and 2½ grains (0.12 to 0.16 Gm.) until 25 to 30 grains (1.7 to 2.3 Gm.) is given. This amount is usually sufficient to cure an adult; the children are given proportionately smaller doses, the maximum dose being on the basis of 0.003 Gm. per kilo of body weight. Treatment must be proceeded with cautiously, as some patients show a pronounced intolerance of the drug.

It is advisable that the patient should remain in a recumbent position for at least one hour after each intravenous administration. The drug has a depressing effect on the heart, circulation and respiration. The blood pressure falls while the pulmonary pressure rises.

The antimony is slowly excreted and has a cumulative action. After toxic doses, fatty degeneration of the liver, kidneys and heart may be present, with congestion of the dura mater and cerebral vessels. According to Khalil, the principal organ of excretion is the kidney. In patients with cardiac, pulmonary and hepatic disorders, the drug is usually contraindicated. While sudden death has sometimes occurred, the deaths from its administration are said according to some statistics to constitute only about 0.1 per cent. Mainzer and Krause (1939), have made electrocardiogram studies of 12 patients during antimony treatment. In 7 cases considerable pathological alterations were found and changes of the S.T. interval, as well as in the T deflection. The abnormalities, they considered, were due to intoxication of the heart muscle from the antimony, though the process in most cases was not clinically evident.

Usually following treatment with antimony, a rapid improvement in the condition of the urine is observed, all traces of blood disappearing. In Egypt, Khalil has recommended a 6 per cent solution for use. The course consists of 12 injections, given 3 times weekly until 22½ grains of the drug have been administered. It occupies 4 weeks. Fairley has confirmed the specific action of tartar emetic, especially in its effects in *S. spindalis* infection of goats, and has shown that it is capable of killing off the adult bilharzia parasites and eradicating the disease.

The pentavalent compounds of antimony, as neostibosan and neostan do not seem to be as efficacious as tartar emetic.

Fouadin (Neoantimosan) (Bayer).—This is a trivalent compound antimony pyrocatechin disulphonate of sodium (containing 13 per cent of antimony), which was

introduced in 1929 especially for the treatment of bilharziasis in Egypt. The drug is administered intramuscularly on alternate days and is said to produce no local irritation or sloughing at the site of the injection. It usually causes no nausea or vomiting, coughing or rigors. According to Khalil, the whole course of the drug consists of the intramuscular injection of the 7 per cent solution as follows:

1st day	1.5 cc.
2nd day	3.5 cc.
Then on alternate days	
3rd day through 17th day	5.0 cc. each

It is claimed that a cure may be effected in 19 days. Fifty per cent of the drug is excreted in the urine, and 4 per cent in the faeces. Khalil (1930) treated 1479 cases with fouadin and states that the cure was obtained in 97.6 per cent.

Diamantis (1938) emphasizes that there are many deaths which occur annually in Egypt from the use of fouadin and points out the necessity of giving a mixed antimony and emetin treatment in quantities which are below the lethal dose of each.

Other authors believe that treatment with tartar emetic is more effective. Other drugs that have been particularly recommended for treatment are emetin and anthiomaline.

Tyskalas believes that when emetin is given intravenously (in doses of 1 to 1.5 gr.) that it is superior to every other specific. However, toxic symptoms, diarrheoa, vomiting and neuritis are apt to ensue when the drug is given intravenously. Tyskalas, however, has also reported good results from injections of the drug intramuscularly in doses of 1½ gr. daily, the total course lasting 10 days to 2 weeks.

Anthiomaline, a lithium salt of antimony, has been recommended particularly by Moulinard and by Cawston, but it has not yet been widely employed.

Ashkar (1938) has reported on the treatment of 24 patients with urinary schistosomiasis with this drug, in 6 per cent solution. The drug was found to be more toxic than fouadin and to give rise to unpleasant symptoms in some of the cases, but the results of the treatment of the majority after from 6 to 9 injections were favorable. In one patient, the ova were still being passed after the ninth injection.

Local Treatment.—For the treatment of the urinary calculi and new growths in the bladder, surgical intervention is sometimes necessary. When cystitis and distress are extreme, perineal caecostomy and drainage may give relief. Perineal fistula and stone and stricture may also require relief by surgical operation.

II. Schistosomiasis (Bilharziasis) Produced by Schistosoma Mansoni

Definition.—A chronic disease produced by *Schistosoma mansoni* characterized by intestinal lesions frequently resulting in dysenteric symptoms and by visceral complications which may give rise to splenomegaly and to cirrhosis of the liver.

History and Geographical Distribution

History.—In 1851, Bilharz observed lateral spined eggs in some female Schistosomes found at autopsy of an individual dying in Cairo. Sonsino and Manson, who also observed lateral spined eggs in female worms, suggested that a distinct species was concerned. However, Looss was opposed to such a hypothesis and it was suggested that the peculiar position of the spine of the ovum was due to distortion of the egg-shell either in the fluke or in passing through the muscular coat of the rectum. In 1903 Manson found lateral spined eggs in the faeces of a patient from Antigua, West Indies, who had never suffered from haematuria, which led him to think that the infection was a distinct one. In 1907, Sambon on the basis not only of differences in the character

of the egg-shell from that of *S. haematobium*, but also on account of the clinical picture produced by the parasite and different geographical distribution, created the species *S. mansoni* for this parasite. Later he reported upon many cases of lateral spined schistosomiasis from South America.

Holcomb and Da Silva (1909) first described the peculiar anatomical distinctions of *S. mansoni*. The autopsy studies of Flu (1911) and Risquez (1918) further substantiated the idea of a different species. Leiper (1916–18) finally proved experimentally the distinctions between *S. mansoni* and *S. haematobium*, demonstrating that the miracidia hatched from lateral spined eggs developed in Egyptian snails of the genus *Planorbis* and not of the genus *Bulinus*, and also that there are constant morphological distinctions between *S. mansoni* and *S. hematobium*.

Geographical Distribution.—It has been suggested that *S. mansoni* was originally a West African species.

Its geographical distribution includes the Nile Valley and the upper Sudan and along the East African Coast from Zanzibar to the Zambesi river, extending inland to northern Rhodesia, Tanganyika and the Belgian Congo. A few cases have also been reported in Natal and in the Transvaal and Madagascar. In West Africa, its distribution extends through Senegal and French Guinea to Lake Chad. It has also been found in Liberia and Sierra Leone. Van den Berghe (1939) has found it common throughout the Belgian Congo, and generally distributed at all altitudes below 1500 meters. The only cases reported in Asia are the few in Arabia, at Yemen.

In the western hemisphere it has been suggested that the infection was probably introduced originally by African slaves. It occurs especially in northern Brazil, and Davis (1934) who made a study there of specimens of the liver obtained with the viscerotone found evidences of infection in 1594 sections. Martins and Dos Anjox (1939) believe that the infection has been recently introduced in Northeastern Brazil, where they found in the Province of Minas Geraes an incidence of from 3 to 85 per cent in different localities. It has also been reported in earlier years in Venezuela and more recently in that country by Mendoza (1936). Scott (1940) found in mountain valleys near Caracas at least 70 per cent of the rural population to be infected, including practically every male over 10 years of age. He believes that schistosomiasis in Venezuela is as severe as anywhere in the world.

It is also common in Dutch Guiana. Faust and Hoffmann found it in numerous localities in Puerto Rico and it has been suggested that it occurs in Santa Domingo. Cameron, in 1932, found a quarter of the population of St. Kitts to be infected, where he also found the infection common in the West African green monkey, *Cercopithecus sabaeus*. The infection is also common elsewhere in the Antilles, notably at Antigua, Guadaloupe, Martinique, St. Lucia, Nevis, Monserrat, and Vieques.

Etiology

Morphology and Life History.—Schistosoma mansoni (Sambon, 1907) in its adult stage resembles *S. haematobium*, but it is generally smaller in size and more grossly tuberculated. In *S. mansoni*, the female usually deposits only one egg at a time, but probably produces from one to several hundred eggs per day. The eggs are somewhat spindle-shaped and provided with a lateral spine and they are generally slightly shorter than those of *S. haematobium*. The adult male parasite measures from 6.4 to 9.9 mm. long and the female 7.2 to 14 mm. long. The testes of the male number 6 to 9. In the female, the ovary is in the anterior half of the body and the uterus is comparatively short. It is probably for this reason that it only deposits one ovum at a time. The

gut branches reunite in the anterior half of the body. The eggs which are usually passed in the faeces, rarely in the urine, measure 114 to 175μ in length by 45 to 68μ in breadth. They have a yellowish-brown transparent shell and a characteristic lateral spine. The sexually mature worms are found in the human body, particularly in the mesenteric venules which drain the large intestine and the posterior segment of the ileum, sometimes in the upper branches of the superior mesenteric vein, the vesicular plexus, and within the intrahepatic portion of the portal veins. The sexes are often found separately, in contrast to what is usual with *S. haematobium.* However, at the time of oviposition the females are held by the males in the gynecophoric canal in the small venules adjacent to the intestinal wall. The ova are deposited directly in the venules of the colon and especially of the rectum, frequently in the submucous layer of the intestine. Rarely they may be deposited in the venules of the bladder. The ova soon break out of the vessels and are discharged into the lumen of the intestine. In other instances, lying in the submucosa they give rise to inflammatory processes resulting in the formation of pseudotubercles or of small abscesses. The ova are also carried in the portal stream into the liver and here in the periportal tissues also occasion inflammatory reactions. A large number of them passing through the intestinal wall are discharged with the faeces containing blood and mucus. Shortly after their passage, the eggs, which are usually mature, hatch through a rift in the shell, and the miracidia, which are larger than those of *S. haematobium*, escape. In water, the free-swimming period does not usually exceed 16 hours, and to survive, the miracidium must pass in this time into the molluscan intermediate host.

The life cycle within the snail is parallel to that of *S. haematobium.* Under favorable conditions, a minimum period of 4 weeks is required. When the cercariae escape from the snail, they resemble those of *S. haematobium.* They attack and invade the skin of the human host and migrate through the blood stream to the intrahepatic portal stream in a similar way to *S. haematobium.* However, Faust and Hoffman have found that in experimental infections of animals the metacercariae of *S. mansoni* are not immediately filtered out on their arrival in the liver and usually pass through the hepatic capillaries into the lungs and general circulation from one to several times, before finally accumulating in the portal stream. The incubation period in the human host is about 7 weeks.

The mature worms sometimes first oviposit in the ileo-colic and colic branches of the superior mesenteric vein and the colic branch of the inferior mesenteric, later wandering downward into other anastomoses of the venous circulation. Day (1937) has found that the adult worms may rarely migrate by the accessory portal circulation and be carried to the pulmonary arterioles. Lesions of the lungs are common complications of the infection.

Intermediate Hosts.—The intermediate molluscan hosts which are known include *Planorbis boissyi* (Egypt and Italian East Africa); *P. alexandrinus* and *P. herbeni* (Sudan); *P. pfeifferi* (Natal, Southern Rhodesia, Sierra Leone); *P. sudanicus* (Nyasaland); *P. adowensis* (Belgian Congo); *Australorbis glabratus* (formerly *Planorbis guadaloupensis;* little more than a subspecies) (Venezuela, Lesser Antilles, Puerto Rico); *A. olivaceus* and *A. centimetralis* (Brazil), and *A. antiguensis* (Lesser Antilles). In addition, *Physopsis africana* and *Bulinus tropicus* have been incriminated in Natal. Martins (1938) states that *P. guadaloupensis*, *P. olivaceus*, *P. centimetralis*, *P. nigricans*, *P. immunis*, and probably *P. peregrinus* are the same species as *Australorbis glabratus.* In any case, it appears that *Australorbis* is little more than a subgenus of *Planorbis* (Chandler, 1940). Scott, (1942) has found *Australorbis glabratus* to be the infecting snail in Venezuela.

The species of *Planorbis* which occur in North America, Europe and the Orient belong to different groups from those in Africa and tropical America and may not be capable of serving as intermediate hosts of human infection.

Epidemiology

S. mansoni apparently requires somewhat different conditions for its propagation than *S. haematobium.* Thus although the two infections

are frequently found associated in Africa, yet the distribution is not identical, but depends particularly upon the distribution of their respective intermediate snail hosts. Also there are areas in the southern Sudan and in West Africa where *S. mansoni* is not uncommon, yet *S. haematobium* is not found at all. While schistosomiasis occurs in 11 of the 14 provinces of the Sudan, *S. haematobium* is the common type in the north, while south of the upper Nile provinces, intestinal bilharziasis due to *S. mansoni* is the only endemic type.

Although monkeys have been found infected in nature and may have been an epidemiological factor in the spread of the disease in St. Kitts, human infection is usually acquired from other human cases of the disease. The infection is commonly disseminated by the deposition of the infected faeces or drainage from them into the water courses which contain the appropriate intermediate mollusc hosts. Sewage from towns in endemic localities that is discharged into streams may also be a source of infection.

In the mountain valleys in Venezuela, when the infection rate is high (at least 70 per cent), Scott (1940) found infection is frequently acquired because of the pollution of canals near dwellings, but random pollution in the fields was also of equal importance.

The disease is acquired by direct contact with water containing the cercariae, the parasite passing through the buccal mucosa by drinking such water or directly through the skin in wading or bathing. Entrance of the cercariae may be effected through the mucous membranes, not only those of the mouth but of the genitalia and anus and even of the nasal mucosa. Experimental infection by mouth has been obtained but because gastric juice may destroy cercariae when brought into contact with it, it seems probable that where cases have occurred from drinking water the cercariae probably immediately traversed the buccal mucous membrane and entered the veins or lymphatic vessels in this way.

In Egypt the infection is acquired especially during the months when the water is sufficiently shallow to permit of a high concentration of cercariae. In the Nile region, the most dangerous period is usually from February to June, but in the case of some of the inland lakes the snail incidence of the disease is from October to the end of January. Infection of the water can frequently not be determined by its appearance. Thus in Northern Nigeria and in Kenya cases of infection have been reported following bathing in clear, limpid pools containing no apparent aquatic vegetation.

Neither sand filtration nor aluminum sulphate clarification will remove the cercariae, although they may be destroyed by chloramine sodium hypochlorite and gaseous chlorine. Witenburg and Yofe state that gaseous chlorine is the only practical method and recommend for this purpose a chloramine solution which contains from 1 to 2 parts per million of active chloramine (see p. 1413).

Pathology

The pathological changes are produced in the intestine by the ova. Owing to their sharp spines and chitinous shells, they act as irritating foreign bodies in the intestinal wall and cause proliferation of the epi-

thelial cells of the mucosa, and an inflammatory reaction, consisting of the formation of pseudo-tubercles in the perivascular tissues and later on small abscesses. By proliferation of the epithelium the mucous membrane becomes thickened and papillomata are often formed which may be very vascular. By rupture of the blood vessels, necrosis of the epithelium and the formation of septic foci in the muscularis and submucosa, ulcerations occur in the bowel wall, sometimes produced by the tearing off of the papillomata through the peristaltic action of the intestine. Eventually well marked ulcers may be produced. In some instances, perforation of the bowel may result. When ulcerations of the papillomata occur in the intestine, symptoms of dysentery arise (see schistosomal dysentery (p. 458).

Fairley, from experimental studies in monkeys, has found the earliest lesions occur as pseudotubercles, small white nodules consisting of fibroblastic cells with large numbers of eosinophiles. Lampe has also observed pseudotubercles in the mesenteric glands in human cases of infection. They may be scattered through all organs, and particularly on the peritoneal coat of the bowel. They may also occur in the mucous membranes, and may be seen with the sigmoidoscope.

In the liver, the ova may be found in great numbers. In some instances in which the disease has been long chronic a form of "pipe stem" cirrhosis may result. Massive congestion may occur. In the advanced stage due to thickening of the large veins of the liver, a periportal fibrous cirrhosis results and ascites is not uncommon unless compensatory dilatation of the collateral venous circulation occurs.

The spleen may also become greatly enlarged, due in some instances to infiltration with ova, but also in some cases more particularly through passive congestion, for in many cases ova have not been found in the spleen. Onsi, however, believes the ova frequently are destroyed in the spleen, and it is for this reason they are not more often detected there.

The ova may also at times escape into the tissues of the lungs, pancreas, kidneys, adrenals, myocardium, and even the spinal cord, and can give rise to inflammatory changes in these organs. Vitug (1941) et al have reported the presence of ova found at autopsy in the brain and intestine, liver and lungs. The patient suffered with convulsions during life. In the lungs, the ova may give rise to embolisms and to small nodules, which have become encapsulated. In severe infections the inflammatory process may become chronic in the lungs and lead to the dilatation of the right ventricle of the heart and death from congestion and heart failure.

In a series of necropsies in Egypt, lesions of the lungs were encountered in one-third, and one-tenth of the deaths were found to be due to this complication. Shaw and Ghareed have pointed out that the lesions are especially due to embolism by ova derived from female flukes outside the lung.

They are filtered out in the arterioles which accompany the bronchioles, producing diffuse arterial changes. Parenchymatous tubules were found containing the characteristic eggs. In some 10 per cent of their cases the adult worms were found in the pulmonary arteries. Girgess has emphasized that serious involvement of the liver and spleen is relatively common, in connection with involvement of the intestine. He attributes the visceral lesions particularly to toxaemia produced primarily or exclusively by male worms. In such cases the ova in the faeces may be few or completely lacking This view has not been accepted by other observers.

Symptomatology

Intestinal Symptoms.—The ova of the parasite deposited in the submucous layer of the rectum and colon frequently gives rise to dysenteric symptoms from 6 to 8 weeks after infection. Pons (1937) in Puerto Rico, found that initial egg extrusion into the intestine occurred from 37 to 44 days after exposure to infection. During this period there is often abdominal pain, frequent stools containing blood and mucus and also lateral spined eggs. In some instances as a result of tissue reaction occurring around the ova deposited in the intestinal wall, the dysentery may become less marked or disappear for a time. However, it usually recurs later. At other times the movements may assume a diarrhoeal character with the evacuation of undigested food. In cases of longer standing, small or large polypoid growths may be felt inside the sphincter ani. They also may protrude from the rectum and may be confused with simple haemorrhoids. Polypoid growths may occur in any portion of the colon as high as the sigmoid flexure. The small intestine is hardly ever affected except in the lower part. Hence in the abdominal examination of the cases with dysenteric symptoms, tenderness is frequently especially marked over the caecum.

General Symptoms.—In the early stages of severe infections, toxic symptoms may be noted. As with *S. haematobium*, there may be an initial dermatitis, even though there is usually no appreciable tissue reaction at the site of entry of the skin by the cercariae. General symptoms which have been noted are a remittent pyrexia with marked abdominal pain, anorexia, rigors, and pulmonary symptoms. There also may be a diarrhoea, suggested as due to the toxaemia. On abdominal examination in the later stages of the disease there is frequently found an enlargement of the liver, as well as the spleen. Pronounced leucocytosis with a high eosinophilia has been reported. In cases of long standing, abdominal tumors may form which are easily palpable, and intestinal stasis or distention may occur. Prolapse of the rectum and infiltration of the tissues with eggs and fistulae are common. After cirrhosis of the liver has developed ascites frequently occurs. Deposition of the ova of the parasite in the appendix may also occur and produce symptoms of a sub-acute appendicitis, as described in infection with *S. haematobium*. Vitug (1941) has found ova at autopsy in the thickened piaarachnoid and in the cortex and white matter below it. The choroid plexus showed many capillaries plugged with ova. The patient suffered with convulsions and unconscious attacks during life.

Symptoms of Visceral Schistosomiasis.—In Egypt and to a less extent in other parts of Africa, *splenomegaly* very frequently follows infection with *Schistosoma mansoni*. In some localities 20 per cent of the infants have been found with splenic enlargement and anaemia. It is common in Egyptian peasants, among the working classes, at all ages up to 30. In the young it may run a severe course, while at a later age it becomes chronic and is frequently accompanied by ascites. This form of splenomegaly was especially described by Ferguson and Day in Egypt and by Richards. in the surgical services at Cairo as amounting to some 12 per

cent of the cases, while in a medical study 5 per cent of the admissions were due to it, males being more frequently affected than females.

The infection, while resembling Banti's disease, usually is associated with fever and severe anaemia. About 16 per cent of the patients noted an attack of diarrhoea or dysentery at the beginning of the illness. The usual complaint on admission was the swelling of the spleen and local pain. In most cases which had suffered for about 2 years, the enlargement of the spleen and liver was progressive, causing eventually a characteristic expansion of the upper abdomen, the costal angle being widely hooked out and the recti muscles separated above the umbilicus, while the heart was often displaced upward. There was sometimes considerable enlargement of the liver, with a moderate splenomegaly. The fibrotic spleen in advanced cases may weigh 5–12 lbs. The spleen on removal is usually found to be firm in consistence. Microscopically a general hyperplasia is evident and there is sometimes a striking phagocytosis of the red corpuscles by macrophages.

According to Day, a few ova of *S. mansoni* may be present. In other instances, the ova may not be found in the spleen. Onsi (1937) however, states that failure to find ova in the spleen may be due to the fact that the spleen rapidly destroys ova deposited in it.

He has recommended for the finding of ova in the enlarged spleen maceration of the tissue in 20 per cent soda solution and subsequent centrifugation. The eggs are often phagocytized by giant cells and numerous eosinophiles may be present in the tissues.

After studying 1400 cases of Egyptian splenomegaly, he believes the splenic enlargement is due to response of the reticuloendothelial tissue of the spleen to deposition of ova in it. As a result there is a cellular response which quickly ends in digestion and removal of the solid remnants (parts of the egg-shell) of the ova. With frequent repetition of the process, under the condition of perpetual re-infection in which the patients live, there is produced ultimately a condition of permanent hyperplasia and fibrosis.

He thinks the splenic enlargement is not dependent on either intestinal or hepatic lesions.

However some authors have emphasized that the number of ova may be very small in either the liver or the spleen and not sufficient to account for the extensive cirrhotic changes seen, especially in the liver. In the later stages of the disease, hepatic lesions are usually prominent and the picture one of multilobular cirrhosis with isolated necrotic foci, sometimes containing ova. In some instances the liver becomes shrunken and adherent to the diaphragm.

The symptoms of *Egyptian splenomegaly* are very varied. There may be irregular fever, wasting, and marked visible anaemia. The spleen, hard and firm, may often reach to the umbilicus. The liver in the early stages is also usually enlarged. Vomiting and diarrhoea are frequent. Intermittent dysentery may also occur. Haematemesis is often present. Jaundice is rare. Vomiting may be a common feature. The blood picture varies at different stages of the disease. In the early stages there may be a distinct leucocytosis. Later, as the anaemia becomes progressive and of the chlorotic type, leucopenia occurs, and there is frequently a mononuclear increase. The patient often succumbs to the hepatic cirrhosis accompanied by ascites and emaciation. Death is frequently due to pulmonary complications.

Pulmonary Complications.—Pons (1937) in Puerto Rico, found cough invariably present in the early cases, and tenderness over the liver, spleen and intestines.

Mainzer (1939) who made a study of serial radiographs in Alexandria, found that in infection with *S. mansoni* latent pulmonary involvement is usually present even in cases with no clinical pulmonary symptoms and that it becomes apparent about 3 months after infection.

He describes the X-ray appearance of the pulmonary lesions as consisting of distinct foci varying in size, density and distribution, increased striation, and unchanged and intensified hilar shadows. Cough, fever and wasting may simulate tuberculosis, and after the destruction of the parasites contracting fibrosis may constrict the bronchioles or vesicles. He believes, however, that bilharzial asthma is an allergic phenomenon depending upon the constitutional factors and substances liberated by *S. haematobium* or *S. mansoni*. It does not depend on lesions of the lungs brought about by the parasite, since pulmonary infection is constantly found in schistosomiasis and the allergic nature of the condition is shown by its association with urticaria and by its hereditary transmission. That it is due to *Schistosome* infection is demonstrated by the parallelism of the course of the 2 conditions and its disappearance after specific therapy.

Among the rarer complications, thrombosis of the portal vein and carcinoma of the liver have been recorded. The disease is usually chronic and may last 20 years or more. Magalhães and Coelho (1941) found in Brazil 8 cases of liver cirrhosis with primary cancer. In 5 of these *Schistosoma mansoni* were present and ova were encysted in the connective tissue. They think the effect due to the toxins of the parasite.

Prognosis

As in infection with *S. haematobium*, it is very variable. In mild infections, it is good, and in such cases the disease is frequently successfully treated. In the cases with hepatic cirrhosis or splenomegaly accompanied by ascites, the prognosis is unfavorable and the patients are not usually greatly improved even by intensive treatment with antimony. In such instances, the disease is usually chronic and some of the patients may live for years. In cases with ulceration of the intestine, extensive papillomata of the rectum and dysentery, the prognosis is usually unfavorable. Death is also sometimes due to pulmonary complications.

The diagnosis of *Schistosoma mansoni* infection is made by finding the characteristic lateral spined eggs in the faeces. They may be seen under a low power of the microscope. In about 5 per cent of the cases in Egypt, ova may be found in the urine as well as in the faeces. In dysenteric cases, it is usually unnecessary to use concentration methods for the discovery of the ova. Scott (1937) recommends that 3 routine faecal slide examinations be made and that such examinations must be supplemented by sedimentation. He found rectal swabs to be especially efficient for the recovery of the eggs. If only male worms are present in the infection, no ova will obviously be found in the dejecta. In such infections, the examination of the serum by the complement fixation test with a trematodal antigen may be of assistance. (See p. 1412.)

Treatment and Prophylaxis

Treatment is similar to that outlined for *Schistosoma haematobium* (see p. 1415). On account of the extensive involvement of the liver which may be present in the infection with *S. mansoni*, it should be borne in mind that intolerance to antimony may be great. Some observers

believe that infection with *S. mansoni* is more difficult to cure than that with *S. haematobium.*

Zye and others have employed rectal injections of tartar emetic and reported that they are especially advisable for small children, who take 16 grains by rectum (1 grm.) without toxic effects. The amount of the drug absorbed is not known. Five to seven daily injections have been recommended.

Khalil has employed fouadin extensively in the form of intramuscular injections, but it has not appeared to be as efficacious as tartar emetic. A few cases of sudden death occurred after treatment and he believes that idiosyncrasies to the drug may occur. The rate of renal excretion is most important, and any degree of kidney damage is a contraindication to its use. Usually after 5 injections only dead ova were found in the faeces. According to Egyptian statistics in 1934, of the total number of cases which received 9 or more injections of Fouadin, numbering 1,938, fifty three per cent were cured, 21 per cent required 11 injections, and the remainder required even more. After 13 injections, signs of drug intolerance were noted. Khalil had relapses in 33 per cent of his cases.

Emetin has also been recommended as efficacious. Maciel has recommended 0.6 grm. (about 9 grains) given in a series of 10 injections, the initial 2 injections being ½ gr. and the remainder 1 gr. Emetin treatment is advised for those patients for whom antimony treatment seems inadvisable.

Operative Treatment.—In advanced cases with ascites, the injury to the liver obviously cannot be repaired by specific treatment. Tapping of the abdomen is frequently necessary for relief of the symptoms due to ascites. In early cases, before the development of ascites, Richards, Coleman, Bateman and Stiven have recommended splenectomy for the relief of the splenomegaly and accompanying symptoms. However, the mortality rate in some series has been about 15 per cent. Some of the deaths were due to late shock. Stiven emphasizes that there should be great care in the selection and preparation of the cases for operation. Ascites, heart disease, and debility are contraindicative. Five or six weeks' treatment preliminary to operation is advisable. The weight of the spleens removed by him averaged 3¾ lbs. The favorable effects appeared in many of these cases to be permanent and ascites did not develop. In the early stages Day has found that the splenomegaly may be favorably influenced and the accompanying symptoms disappear after tartar emetic. In cases with extensive disease of the rectum, surgical treatment with excision is frequently advisable.

Prophylaxis.—The problems relating to the prevention and control of the disease are practically the same as have been outlined for *S. haematobium* infection on p. 1413.

III. Schistosomiasis Produced by Schistosoma Japonicum

Synonyms.—Katayama disease, Oriental schistosomiasis.

Definition.—A chronic disease produced by *Schistosoma japonicum*, characterized by chronic dysentery, great enlargement of the liver and

spleen, and subsequent development of ascites, anaemia, and a terminal cirrhosis of the liver.

History and Geographical Distribution

History.—The disease was apparently first mentioned by Fujii in Japan in 1847, and for many years was recognized as an endemic infection characterized by enlargement of the liver, splenomegaly, ascites, cachexia, and dysenteric symptoms. Majima, in 1888 found ova in a cirrhotic liver and in 1904 Fujinami discovered the adult trematode *S. japonica*, in the portal veins of a cat. Katsurada succeeded in communicating the infection to cats by immersing their legs in the water of certain ponds said to convey the disease and first found the adult parasites in infected dogs and cats. The experimental work of Fujinami, Miyagawa and especially of Miyaira and Suzuki (1913–14), demonstrated the life cycle of the organism through the snail and the method of cutaneous infection of man, an observation confirmed the following year by Leiper and Atkinson

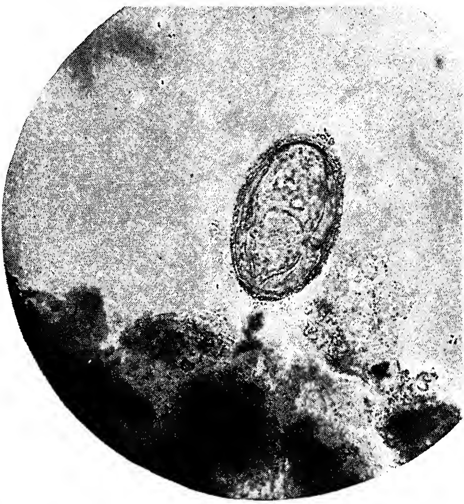

Fig. 341.—Egg of Schistosoma japonicum containing the ciliated larva or miracidium from fresh faeces of man. (Photo. Pathological Institute, Batavia, Java.)

Geographical Distribution.—Its distribution is apparently confined to the Far East. It is common in certain districts in China, and practically the whole Yangtse valley is infected. Faust has estimated that in China tens of millions of people are yearly exposed to infection.

In addition to the Yangtse basin, the coastal areas and the Mekong valley are serious endemic foci. Recently an endemic center has been reported at Shiuchow on the north river, near Canton, and also at Foochow (Fukien). It has also been found on the Burmese border. In Japan, 5 comparatively small foci are known, it being especially prevalent in the province of Hiroshima and in the village of Katayama. The disease has also been found in Formosa and in the southern Philippine Islands of Leyte, Samar and Mindanao. An area of infection has also been found by Brug and Tesch (1937), in the Celebes.

Morphology.—The parasites resemble *S. haematobium* and *S. mansoni*, but lack the tuberculations of the integument. Also the acetabulum or ventral sucker is larger and

stouter than in these species. The males measure 12–20 mm. The cuticle is relatively smooth, but is covered with minute acuminate spines. Their sides infold more markedly than do those of the preceeding species. Usually 7 testes can be distinguished. The females average about 25 mm. in length and their integument is also covered with minute spines. The ovary lies just posterior to the middle of the body. In both sexes the gut branches reunite in the posterior fork of the body. The uterus consists of a long, straight tube containing as many as 50 ova at one time. The ova are oval, transparent, and when passed in the faeces measure about 70–90μ by 50–60. They have a smooth shell but usually show a rudimentary or lateral spine or knob near one end. Red blood cells and other tissue cells are sometimes seen adherent to the shell. The eggs are excreted only in the faeces.

Transmission.—The eggs when passed in the faeces are usually mature and when water is added to the faeces they hatch, the miracidium escaping through a rent in the shell and swimming about in the water. It closely resembles that of *S. haematobium* and differs only in its somewhat smaller size and in certain minute internal structures.

On reaching a suitable snail it enters the soft tissues of the mollusc and in the course of 5–7 weeks undergoes a two-fold multiplicative process, with the successive production of first and second generation sporocysts with typical forked-tailed cercariae, the structure of which also is almost identical with that of *S. haematobium* and *S. mansoni*. An important differentiating characteristic, however, is the presence of 5 pairs of penetration glands. On contact with the skin of the mammal, the cercariae lose their tails and in the course of a short time penetrate into the capillaries of the skin and enter the venous circulation, being carried through the right heart to the lungs and thence to the pulmonary capillaries and the left heart, into the systemic circulation. According to Faust (1940) only those individuals which reach the intra-hepatic portal circulation via the mesenteric artery and capillaries grow and migrate out to the venules of the superior and mesenteric vessel. Within 5 weeks the parasites have mated and the females are laying ova.

Molluscan Hosts.—The appropriate snails which are known to serve as the intermediate host for *S. japonicum* in Japan and along the coast of China are, according to Bartsch (1936) various species of *Oncomelania*, *Katayama*, and *Schistosomophora*. Faust lists the following: *Katayama nosophora* in Japan and along the coast of China; *K. formosana* in Formosa; *Oncomelania hupensis* in the Yangtse Basin; *O. hydrobiopsis* (Syn. *Blanfordia quadrasi*) in Leyte, Philippine Islands. There is still much discussion about the nomenclature of some of these species. Snails of this group are only 7–10 mm. long, with high spired shells and are operculated.

Epidemiology

The parasite is by no means confined to man, but infects naturally cats, dogs, cattle, horses and pigs, goats and sheep, among domestic animals, and also field mice. Cattle and water buffaloes are also important reservoir hosts in certain endemic foci.* Faust (1940) reports that congenital infections have occasionally been recorded for man.

The disease is acquired by man similarly as in *S. mansoni* infection, by direct contact with infected water containing the cercariae.

Pathology and Symptomatology

The course of the disease may be divided into 3 stages: (1) the incubation period, in which urticarial, pulmonary, and febrile manifestations may be present. This stage may last for about a month; (2) that of deposition and extrusion, when the ova appear in the bloody mucus stools; and (3) the period of further tissue destruction and proliferation, which may be eventually characterized by cirrhosis of the liver, ascites, cachexia and death.

* Bonne (1942) *et al* in the Celebes found that the village dogs used in hunting pigs were infected with *S. japonicum* as were the wild deer.

In the first stage, there may be headache and an evening rise of temperature to about 101°F. or 102°F. Shortly after the onset, urticarial lesions sometimes 5 or 6 centimeters in diameter may appear and disappear on various parts of the body. This condition has been termed kabure. The urticarial rash, accompanied by fever, may develop as early as the fifth day after exposure. It may be accompanied by oedema of the subcutaneous tissues and the wheals may be present both in the skin and sometimes in the mucous membranes. The pulse rate is usually low. Very characteristic and early manifestations are those of pulmonary involvement. Here oedematous patches may give on auscultation signs of crepitation and consolidation and these may rapidly disappear and reappear in another part of the lungs.

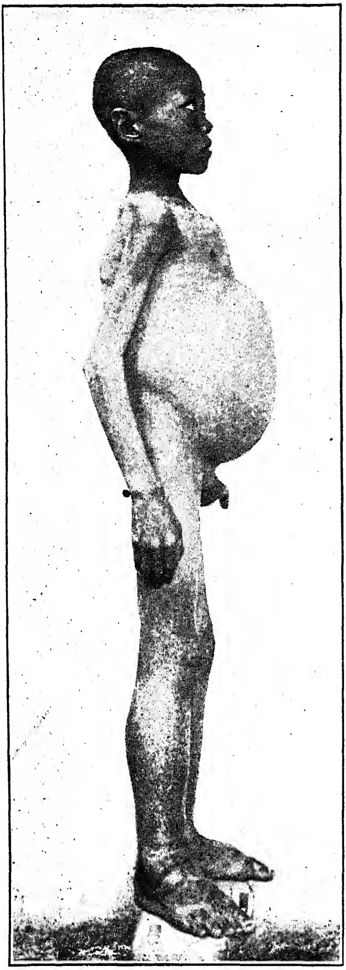

FIG. 342.—Case of *Schistosoma japonicum*. Severe infection of three years' duration. Ova very abundant in stools. Liver dullness diminished. Spleen not enlarged. (From Jefferys and Maxwell.)

The pulmonary manifestations and associated fever sometimes have caused a diagnosis of broncho-pneumonia to be made. A dry hacking cough appears early and with the fever may cause one to think of tuberculosis. The urticarial lesions have caused a diagnosis of ptomaine poisoning to be made. The blood examination may show a leucocytosis and a marked eosinophilia, of from 30 to 60 per cent. A toxic diarrhoea generally develops toward the end of this period.

The second period, beginning with the deposition of the eggs in the tissues comprising the wall of the intestine and their discharge into the lumen of the bowel, is frequently accompanied by a profuse dysentery. The eggs in the faeces are sometimes surrounded by a layer of cellular debris. At this period, there may be recurrent daily fever, epigastric pain with tenderness over the abdomen, and large, tender liver and spleen, and loss of appetite and weight. The acute attack often terminates in from 3 to 10 weeks, when the fever often subsides and the other symptoms ameliorate. Exercise may cause exacerbation of the intestinal symptoms. The blood picture frequently changes from that of the previous one of leucocytosis and eosinophilia to that of a secondary anaemia with erythropenia, leukopenia and reduction in the eosinophile count.

These symptoms are apparently due not only to the infiltration of the ova in the tissues of the intestinal wall but into the periportal tissues of the liver and other organs where pseudotubercles and abscesses may develop around the ova. Hoeppli believes that the irritation caused by the eggs is not only mechanical, but chemical as well, and that the discharge of secretions occurs through the shells of the eggs still lodged in the tissues. Giant cells frequently develop within the pseudo-tubercles which later become encapsulated by fibrous tissue. In the liver, spleen and lymph nodes endothelial cells are frequently seen containing haematin pigment. During these inflammatory changes in the liver and spleen the fibrous reticulum becomes increased and these organs gradually become greatly enlarged. The mesenteric lymph nodes also become swollen. Changes in the viscera are usually much more marked in *Schistosoma japonicum* infection than in that due to *Schistosoma mansoni*, because the infections with the former are usually much more severe and the daily output of eggs by the corresponding parasites is much greater. Also there is greater proximity of the parasites to the liver when they are present in the superior mesenteric veins.

The third period of tissue proliferation gradually develops. The liver gradually diminishes in size as its parenchyma cells are replaced by fibrous tissue. The spleen, however, continues to enlarge, especially on account of the circulatory congestion. Ascites is a very common development, and especially depends upon the amount of hepatic cirrhosis. In the bowel wall abscesses frequently develop around clusters of the ova, with the development of papillomata, and later ulcerations are formed. Finally the intestinal wall may become greatly increased in thickness and later on contractions from fibrosis may occur.

The male and female worms are often found together in the distended veins of the submucosa, for in this species the females do not leave the gynocoporic canal of the male when laying eggs but merely move forward in it (Chandler, 1940).

When the intestinal walls become thickened, more and more ova are swept back into the liver. Yamagiwa has pointed out that the ova may cause embolic closure of the portal vessels and may serve as an additional factor in the production of the portal cirrhosis. In some instances the ova may reach the lungs, bladder, or even the capillaries of the brain. They have also been found in the lymph nodes. Africa and Santa Cruz (1939) have also found the ova in the myocardium where a large number of eggs were found in typical pseudotubercles in the intraventricular septum of the heart. Sections of the heart showed under the low power a close resemblance to tuberculosis on account of the presence of numerous giant cells. Ova were also found in the intestinal wall, liver, lungs, kidneys and brain of this case. Jacksonian fits, hemiplegia, and even total blindness as the result of deposition of the ova in the central cortex and destruction of the visual centers have been reported. Garcia has found the ova in the tissues of a chronic ulcer of the leg of a child in the Philippines. Ova were also present in the faeces.

The third or final stage of the disease may not occur until 3 to 5 years after infection. When the liver and spleen become markedly cirrhotic

ascites and oedema of the extremities is common, together with anaemia and exacerbations of the dysenteric symptoms. The patient may finally die of exhaustion or some terminal infection.

Prognosis

In severe infections with *S. japonicum* the prognosis is unfavorable unless treatment can be given fairly early in the disease and before the visceral lesions are well advanced. In fact, in very advanced stages with cirrhosis of the liver and splenomegaly and ascites, treatment is usually ineffective and the patient eventually dies of exhaustion or some terminal infection.

Diagnosis

Specific diagnosis depends upon the discovery of the characteristic ova in the faeces. They are often found in the adherent mucus. When not numerous, the faeces may be emulsified, strained, and sedimented, and the sediment examined for ova. Flotation methods are unsatisfactory.

Fülleborn suggested washing the sediment 2 or 3 times with 2.5 per cent salt solution, and each time allowing the eggs to sediment 5 minutes in the dark and decanting the fluid. Then distilled water is added to the preparation and exposed to the light at a temperature of 120°F. The miracidia hatch quickly and by using a hand lens may be seen swimming about near the surface. Those of *S. haematobium* however do not rise to the surface.

In the first stage of the disease the eggs may not be present in the faeces. In such instances, a positive compliment fixation test as devised by Fairley and described under S. haematobium diagnosis, may be of value.

The presence of eosinophilia and evidence that the patient has lived in an endemic area may also suggest the diagnosis.

In later stages of the disease, where the ova cannot be found in the stool, Faust and Meleney have suggested that the aldehyde or serum globulin test is strongly positive in many cases.

The disease in its terminal stages must be differentiated from Banti's disease and from Kala azar. The dysentery must be distinguished especially from the amoebic or bacillary form and from intestinal tuberculosis. The hepatic symptoms may sometimes suggest amoebic liver abscess.

Treatment

Treatment with antimony tartrate has been found equally efficacious in killing off the adult parasites as in the case of *S. haematobium* infection. According to Faust and Meleney, 22–30 gr. of intravenous tartar emetic over a period of 18–20 days is usually curative in the early stages of the infection. Cawston first reported intramuscular injections of the sodium salt as successful in the treatment of schistosomiasis of Asiatic origin. Since antimony by vein is contra-indicated in patients with advanced hepatic cirrhosis as well as in those with anemia, heart disease or nephritis it may be more advisable to employ emetin hydrochloride in some cases.

As a result of the experimental studies on *S. spindalis* infection of the goat, Fairley found that emetin given intravenously in 10–15 injections, varying between 0.7 and 1 mg. per kilo of body weight, caused the rapid death of the parasites and was more efficacious than tartar emetic.

Tyskalas claims that emetin given intravenously in doses of 1½ gr. daily for 10–14 days is superior to every other specific. However, toxic symptoms, diarrhoea, vomiting and neuritis are apt to occur.

Fairley also found in goats that fatal verminous thrombosis of the pancreatic and portal veins might occur as the result of the presence of dead parasites.

In the treatment of the splenomegaly, splenectomy has been employed to some extent but so far with little success, as in most cases the hepatic cirrhosis has usually been well advanced at the time of the operation.

FIG. 343.—Colon from a case of Japanese schistosomiasis showing a marked polypoid condition of the intestinal mucosa. (Army Medical Museum photo No. 39343.)

PREVENTION

The disease is primarily confined to rice farmers and canal boat-men in the endemic areas in the Far East. However, persons bathing or wading in the irrigation ditches, canals and pools are also exposed and may contract the infection. Sportsmen occasionally become infected in snipe shooting in the endemic areas. The urban population are not seriously endangered except when through flood the infected snails may pass through and contaminate the water supplies of towns and cities. It should be borne in mind also that dogs and cattle in China may serve as reservoirs, and in Japan field mice may be important sources of infection.

For prophylaxis, the water suspected of being capable of causing the disease should be boiled or avoided for drinking or bathing purposes. Sportsmen and others finding it necessary to wade in such water should wear long boots. The sterilization or sanitary disposal of the faeces of the cases of schistosomiasis should be carried out where practicable. The cercariae die in 3 to 4 days in stored water. The control problem is more complicated than in schistosomiasis due to *S. mansoni* on account of the common use of human night soil for fertilizer in most of the endemic areas. Attempts should be made to allow the night soil to ripen longer in containers, or to disinfect it with fertilizer salts, as ammonium nitrate, in order to kill the ova before the fertilizer is spread on the fields.

Another important point in the control measures relates to the type of snail. All the species that serve as the intermediate host are amphibious in habits and can withstand desiccation for a month or more. In circumscribed endemic areas the Japanese have reported some success in eliminating the snails by spraying them with live steam and by lining the irrigation ditches. According to Naragayashi, lime in a solution of 1:1000 is the most economical reagent for the extermination of the snails and kills the cercariae in 30 minutes. In the very extensive endemic regions in China, however, the actual location of the infected snails is rarely known and hence antimolluscan campaigns are not practicable.

Rarer Schistosomal Infections of Man

Schistosoma bovis (Sonsino, 1876); syn. *S. matthei* (Veglia and LaRoux, 1939) *S. curassoni* and *S. rodhaini* (Brumpt, 1931) is a not uncommon parasite for sheep, goats cattle and other herbivorous animals in Africa, southern Asia, and parts of southern Europe. It has been reported for man in a few instances in the Belgian Congo, Southern Rhodesia, and Natal. The eggs are discharged in the faeces and resemble those of *S. haematobium*, but are usually longer and narrower, measuring according to Price 160–180μ long by 46–70μ. Unlike *S. haematobium*, this species apparently affects only the intestines. The intermediate snail hosts are the same as those for *S. haematobium*. Dodeswell, 1938, has found that in Kenya Colony *Physopsis nasuta* is susceptible to infection.

Schistosoma spindale (Montgomery, 1936) is a common parasite of cattle, sheep and goats, especially in India and the East Indies and in South Africa. It develops in a species of *Planorbis*. The parasite sometimes inhabits the mesenteric veins of animals and sometimes causes a "snoring disease" in cattle, where by its localization in the nose it produces lesions somewhat similar to those in the intestine or urinary system. A few cases of human infection have been reported in South Africa, where ova were found in the patient's urine. The ova of *S. spindale* are spindle-shaped and often flattened or bowed on one side. The measurements which have been given by Faust (1940) are from 364–400μ in length by 68–72 in width. Porter gives the measurements of those she found in the urine of man as 163–258μ long by 46–70μ wide.

Schistosoma intercalatum (Fisher, 1934).—Chesterman pointed out that at Yakusu near Stanleyville in the Belgian Congo intestinal bilharziasis is the only form of the disease which occurred and that the cases showed only terminal spined eggs somewhat more elongated than those typical of *S. hematobium*. Fisher, who studied these ova, believed they belong to a different species. He found the ova relatively longer and more slender, with a well developed spine, and that they might attain a length of 200μ. The terminal spined ova found in faeces in the Belgian Congo by the writer and Sandground measured between 162 and 169μ in length and from 54 to 64μ in width. Thus they were only very slightly longer than the measurements given by Price for *Schistosoma hematobium* eggs, 120 to 160μ in length by 40 to 60μ in width, and they are evidently much shorter than the ova of *S. spindalis*. Van den Berghe (1939) has found variations in the shape and size of the eggs of *S. intercalatum* and states that they barely exceed in size those of *S. haematobium*. He believes that its local geographical distribution and its limitation to the intestine would seem to be the only factors justifying its being placed in a subspecies.

In Yakusu, the parasite has been reported to infect about 50 per cent of school children. The symptoms are usually of mild dysentery, abdominal pain being only rarely complained of. However, sigmoidoscopic examination in some cases has revealed sandy patches but neither polypi or ulcers have been noted.

S. incognitum.—Chandler (1926) has reported a small *Schistosome* egg with a subterminal spine in supposedly human faeces in India. Both the eggs, which were ovoidal, and the parasites themselves were subsequently found by Saunders (1934) in Indian pigs.

Schistosoma Dermatitis

When the cercariae of the human *Schistosomes*, or the *Schistosomes* of some other animals, penetrate the skin, they may or may not cause an itching rash or a dermatitis. In Puerto Rico, *S. mansoni* may cause a severe prickling sensation when penetrating but usually no subsequent rash. In Egypt, as noted, both *S. mansoni* and *haematobium*, and in the Far East *S. japonicum*, are known to produce urticaria or itching papules and sometimes oedema. In the Far East, however, *S. japonicum* frequently gives rise to no dermatitis.

Cort (1928) however, demonstrated that certain non-human *Schistosome* larvae incapable of infecting man will nevertheless cause a severe dermatitis or swimmer's itch when they penetrate the skin of bathers or waders. As the water evaporated from the skin, a prickling sensation was experienced, followed by urticarial wheals. After about half an hour the initial dermatitis subsided, leaving only a few macules. However, several hours later intense itching developed, with oedema and the transformation of a number of the papules into pustules. The reaction was most intense between the second and third day following exposure. The condition was first observed in Michigan and was found to be common in certain other parts of the north central states and southern Canada. It has also been noted in Germany, France and Wales, while in the Federated Malay States Buckley (1938) has also observed an itching dermatitis in the paddy workers.

At least 8 species of cercariae are known to give rise to these symptoms. Some, however, occur only in marshes and are of no importance. In Michigan, *C. physellae* and *C. stagnicolae*, in Europe *C. ocellata*, and in the Malay States cercariae of *S. spindale* are among those that have been incriminated. Four of the dermatitis-producing species develop in snails of the genus *Lymnaea*, one in *Physa* and one in *Planorbis*.

The affection has attracted increasing attention in the United States, particularly in the lake regions of the north central areas in Wisconsin, Michigan and Manitoba. Brackett (1940) has found that outbreaks of the disease occur most commonly in July and August, although they are occasionally encountered earlier or later in the summer.

Not all persons are susceptible. Children have been more commonly affected, perhaps because their activities in shallower water bring them into contact with more cercariae and, in addition, they may be more sensitive than adults.

Clinically, a few minutes after emerging from infected waters a tingling sensation is felt in the exposed parts of the body. Shortly afterwards, pin point sized red macules may appear. The tingling may then subside and nothing be experienced for a number of hours. Then a distinct itching begins and the macules enlarge to form firm, discrete papules from 2–5 mm. in diameter. They are red first, but may be surrounded by a halo of hyperaemia. Occasionally the lesions become pustular. Secondary infections may cause certain variations. In those very susceptible, urticarial wheals may arise soon after these cercariae invade the skin. The lesions usually fade within a week. The extremities are most frequently involved and the face and neck are usually spared

Vogel (1930) has experimentally infected himself and volunteers with a European species (*Cercaria ocellata*) which is closely related to the *Schistosome* cercariae of the United States. Twenty-four hours later, he removed some of the tissue for histological

study. In one instance, 11 cercariae were found in the tissue, which was sectioned serially. The parasites were found lying in tunnels in the epithelial layer and were still easily recognized. Brackett has also made histological studies, in which the inner surface of the forearm was exposed to *C. elvae*. Biopsy was performed after 29, and again after 50 hours. He observed numerous burrows in the epithelium and evidence of an acute inflammatory reaction, but was unable to find any cercariae. Brackett believes the cercariae were absent in his tissues not because they had gone deeper or been overlooked but because they were destroyed 29 hours after they had entered. Brackett found evidences of an acute inflammatory reaction around the tunnels which the cercariae had apparently temporarily occupied. The acute inflammatory response to the presence of the cercariae was evidenced by pronounced oedema and extensive early infiltration of neutrophiles and lymphocytes. Later extensive invasion with eosinophiles occurred. Clinically, evidence suggested that recovery then follows rapidly.

Brackett's observations show that the dermatitis producing schistosome cercariae of the United States do not continue their development in the skin or set up a systemic infection in man.

In order to obtain information concerning the suitability of primates as hosts of *Schistosomatium douthitti* (Cort, 1914) Brackett exposed the extremities and face of a young female rhesus monkey to the penetration of cercariae and noted a very mild dermatitis on the exposed areas. Three weeks after the last exposure, the animal was autopsied but no trace of the schistosome infection was seen. He assumed that if this parasite, which develops readily in a wide variety of laboratory animals, developed readily in man, it probably would have been found in the one monkey used.

More recently, Penner (1941) has exposed 3 rhesus monkeys at different times of the year to the cercariae of *Schistosomatium douthitti*. In the first, the exposures were light and a mild dermatitis was produced. The monkey was autopsied 4 weeks after the last exposure and on complete and careful examination was found negative for *Schistosoma*. The second young monkey was submitted to severe cercarial exposure the number being estimated at 28,000. He showed signs of distress and scratched himself considerably from a short time after exposure until the time of the autopsy, 5½ days later. A marked dermatitis was then evident. On autopsy, the migrating worms were found to be abundant in the lungs, and slight haemorrhages were noted. The third experiment in a rhesus monkey showed that a mild dermatitis developed, which rapidly disappeared. An autopsy could not be conducted on this animal to see if further development occurred. Penner suggests that the one positive experiment suggests the possibility of penetration of the skin of children who swim in infested areas where the cercariae are abundant.

Treatment.—After penetration, the only possible treatment is by soothing applications. Brackett (1939) recommends as a useful prophylactic wiping with a towel immediately after coming from infested water, since apparently the cercariae penetrate the skin of human beings largely, if not entirely, when the water has evaporated.

Prevention.—Cort and others have reported a satisfactory elimination of the snails from certain districts by an initial dose of copper sulphate at a concentration of 2 parts per million. It may be necessary to treat the body of water again at regular intervals, since after each treatment sometimes snails have been found indicating that at least some of them resisted one or several exposures to the chemical.

Brackett has suggested the use of copper carbonate, on account of its low solubility. He points out that even in the presence of an excess of the compound there might be enough copper in solution to kill snails but not enough to injure fish life. Copper sulphate or copper carbonate has been recommended for the destruction of the snails in small bodies of water. No practical method for use in large lakes is known.

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Chapter XLVIII

HEPATIC, INTESTINAL AND PULMONARY TREMATODE INFECTIONS

CLONORCHIASIS

Definition.—Infection with *Clonorchis sinensis*, leading sometimes in chronic cases to sclerotic changes in the liver.

History.—Cases of infection with *Clonorchis sinensis* have not infrequently been detected in Chinese and Japanese travelers, or immigrants, in the United States and Europe, as well as in the Far East. The parasite, termed the "Chinese liver fluke," was first found at autopsy in 1874, in a Chinese carpenter who was residing in Calcutta at the time he died. McConnell, who discovered the parasite in this case in the bile ducts, in 1875 gave a description and published illustrations of it. During the same year the worm was encountered in Japan, but it was not described in that country until 1883, when Baelz described 2 varieties, one of which he thought was harmless but the other pathogenic. However, Kobayashi (1917) and Chen Lang (1924) have shown that while the size of *Clonorchis sinensis* is relatively variable, there is apparently only one species.

Various records of the occurrence of this fluke in Chinese patients abroad were made between 1877–1907, but the first publication of the occurrence of the infection in the endemic areas in China was made by Heanley in 1908.

Distribution.—*Clonorchis sinensis* (Cobbold, 1875) (Syn. *Opisthorchis sinensis*, Blanchard, 1895) is the most important liver fluke occurring in man. Its endemic distribution has been almost entirely confined to the Sino-Japanese areas, where man and other animals have been found to be extensively and naturally infected.

It is a common parasite of fish-eating animals. Of the animals, the cat and dog are very commonly infected, but wild cats, hogs, martens, badgers, minks, and guinea pigs have also been found infected.

Faust has shown that the endemic areas of infection extend throughout Japan, Korea and China (except the northwest), Formosa, and French Indo-China. However, the heavy foci of human infection are confined to the Okayama District in Japan, southern Korea, parts of Kwangtung Province, China, and the Delta of the Red River in Tonkin, French Indo-China. Faust found that the Kwangtung population is fond of eating raw fish, or fish only partially cooked. In other areas, the Chinese usually cook their fish very thoroughly.

H. T. Chen (1934) who has made a survey of the parasites of dogs, mostly from Canton, found that 44.2 per cent were infected with *Clonorchis sinensis;* and 3800 human cases of the disease were observed in these areas. Chandler (1940) reports the human incidence in Canton is 12 per cent. Chen also studied 57 cats from Canton and 32 from Fuchow, and found *Clonorchis sinensis* present in 80 per cent of the Cantonese cats, and in 59 per cent of the Fuchow animals. He believes that cats are the most important reservoir hosts for clonorchiasis in South China. Katsurada (1900–1922) has reported that in central Japan there are certain districts in which it affects from 56–67 per cent of the population. Raw fish is commonly eaten. Mathis and Leger found one-half of the natives on the east coast of Indo-China infected.

Houdemer (1934) more recently called attention to the prevalence of clonorchiasis in Annam. He found the infection locally present in from 1.4 to 40 per cent of human beings, in nearly 11 per cent of dogs, and 33 per

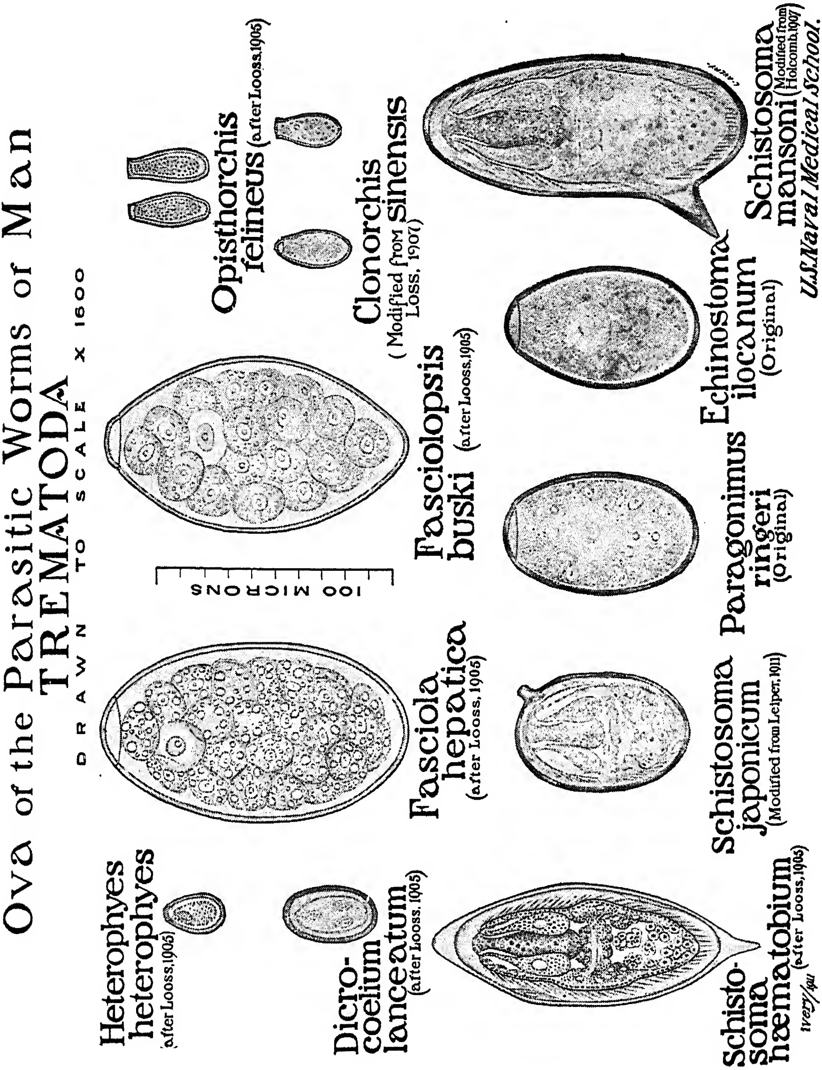

FIG. 344.—Trematode ova.

cent of cats. In this region, the fish are eaten raw, being first cut into pieces 1–4 cm. long. The small species of *Carrasius auratus* usually swims about in a bowl beside the individual when eating. From this bowl the fish is caught up with a small scoop, and the native, after seasoning it, eats it while it is still wriggling.

The extent to which the infection with *Clonorchis* occurs in India is not entirely clear. A few cases of human infection have been reported there, and Chandler found infection very common in cats and dogs in eastern India, but did not find it in man. Acton observed *Clonorchis* ova in the faeces of 2 Indian soldiers in Mesopotamia, and Bagchi (1934) has reported a case of infection in a Mohammedan in Patna. Diagnosis was made by finding the ova in the stools and comparing these with authentic specimens of ova of *Clonorchis sinensis*. He points out that since Indians seldom eat uncooked fish the question is raised whether this infection might not be due to eating raw singhara (*Trapa bicornis*) which is commonly peeled with the teeth. However, further observation regarding this suggestion would seem to be necessary, though Chandler has traced infection with *Fasciolopsis buskii* to eating this singhara.

Binford (1934) has reported upon the occurrence of *Clonorchis* ova in the stools of 4 lepers, none of whom had ever been outside of the Territory of Hawaii. He alludes to the fact that up to 1927 aliens with *Clonorchis* infection were excluded from Hawaii. Since this time, however, the regulation has been relaxed. He states that large quantities of frozen, dried, salted, and pickled fish are imported into the Hawaiian Islands that *Cyprinidae* are known harborers of this infection, and that 2 of the 4 infected persons had eaten raw gold fish (*Cyprinidae*) caught in the artificial taro ponds. In 1907–1908 some 24 cases of infection with *Clonorchis sinensis* (*Opisthorchis sinensis* Blanchard 1895) were reported in the Philippines Islands in Chinese and Filipinos (Strong, Musgrave, and Heiser). Whether the disease is endemic in the Islands appears doubtful.

Itinerant cases of the disease have not infrequently been reported in large seaports. Thus Mayer in 1916 found *Clonorchis sinensis* ova in 40.9 per cent of 200 Chinese sailors who were at the time World War prisoners in Hamburg. Prior to 1927 it was also shown that in the neighborhood of 50 per cent of the Chinese coolies examined by the public health officers in San Francisco were infected with the ova of this parasite, and Shattuck (1923) showed that 54 cases occurred in Boston in Chinese immigrants and in a few Japanese.

The observations of Davis (1934) are of some interest in demonstrating the absence of the infection in Brazil. Thus, at the Yellow Fever Laboratory in Bahia, a microscopical examination was made of sections of pieces of the liver (obtained by the viscerotome) from 25,593 persons who had died in central and northern Brazil. This examination revealed that the presence of the ova of no other fluke was noted except of *Schistosoma mansoni*.

Formerly immigrants found to be infected with the ova of *Clonorchis sinensis* on arrival in the United States were not admitted. Since, however, it is clear from a study of the life cycle of the parasite that there is no likelihood of the infection spreading in this country, this regulation has been rescinded.

Life History and Etiology.—*Clonorchis sinensis* inhabits the bile passages (and occasionally the pancreatic ducts) of man and several other mammals, including the cat, dog, pig, rat, and mouse. The fluke is 10 to 25 mm. long, 2 to 5 mm. broad, pointed anteriorly, and somewhat rounded posteriorly. The integument is aspinous. The oral sucker is slightly larger than the ventral which is situated at the posterior end of the anterior third of the body. The most characteristic features are the deeply lobulated or branched testes, situated one behind the other in the posterior third of the body, the branches extending beyond the intestinal caeca into the lateral fields. When the parasite is squeezed out of the thickened bile ducts it is so transparent and glairy as almost to resemble mucus. Many thousands of these parasites have been found in a single case. The adult flukes have been reported to live for 5 to 20 years.

The ova in the faeces are oval yellowish brown structures, 27–35μ long by 11–20 broad. They contain a ciliated miracidium when passed. This is not liberated until the egg is ingested by the snail. Eggs may be numerous in bile obtained through a duodenal tube, even though sparse in the faeces.

Transmission.—The yellowish-brown ova of *Clonorchis sinensis* are passed in the excreta of man or other infected mammals, and are almost ready to hatch when they leave the mammalian host. Both Saito and Wayson found that under unusual circumstances spontaneous hatching of *Clonorchis* ova may occur. Other observers, and particularly Faust, have shown that hatching of the ova does not take place normally outside the body of the appropriate molluscan host, and in normal development it is necessary for the embryonated egg to be swallowed by the snail. Faust (1930) has shown that the snails which act as the first intermediate host for this fluke are limited to a single subfamily, the *Bithyniinae*, which are represented by four species in the Sino-Japanese area, viz., *Parafossarulus striatulus*, *P. sinensis*, *Bithynia fuchsiana* and *B. longicornis*. The ova after being ingested by these snails hatch in the oesophagus of the mollusc, the miracidium penetrating through the gut wall into the peri-oesophageal

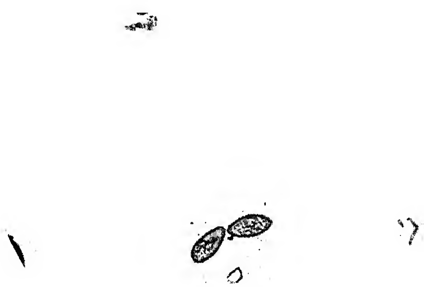

FIG. 345.—Ova of *Clonorchis sinensis*. (After Bell and Sutton from Jefferys and Maxwell.)

lymph space where it metamorphoses into a sporocyst, migrates towards the inter-hepatic lymph sinuses, and there produces a progeny of rediae. These latter in turn produce cercariae. The mature cercariae effect a rupture, first in the tissues of the rediae, then in the taut outer tissue layers of the mollusc, escaping into the water where they swim about vigorously. On coming into contact with fresh water fish the cercariae penetrate under the scales and into the flesh of the fish, in the meantime discarding their caudal appendages.

Faust and Khaw found that practically every species of fresh water fish in China, Japan, Korea, Formosa, and French Indo-China could serve as the second intermediate host for this parasite. Some 40 species of fresh water fish of the families CYPRINIDAE, GOBIIDAE, ANABANTIDAE, and SALMONIDAE have been found infected.

On consumption of the infested raw fish, man or the other mammalian host becomes infected. In the stomach the cysts are digested out of the flesh, and the outer capsule disintegrates. On passing into the duodenum the invigorated adolescaria breaks out of the cyst capsule and becomes attached to the duodenal wall. It next migrates to the opening of the common duct, continuing its course to the biliary duct, and eventually to the biliary capillaries, entering more particularly those of the left lobe

of the liver, due to the fact that the path of migration into this lobe is more direct. Kobayashi (1938) has shown that in cats the young flukes reach the bile ducts 15 hours after ingestion of infected fish and require 26 days to reach maturity.

Pathogenicity and Pathology.—Hoeppli (1933) has examined specimens of the liver from autopsy of 66 Chinese who for the greater part had met a more or less sudden death which was in no case apparently due to *Clonorchis sinensis* infection. With the exception of one case, the infection was always light or moderate. In all the cases the larger bile ducts showed dilatation, thickening of the wall, proliferation of the biliary epithelium and in some instances desquamation, and new formation of bile capillaries with crypt formation in the bile ducts. Only 2 cases of liver cirrhosis were found, one of Laennec's type, the other a portal cirrhosis corresponding to the type of *cirrhosis parasitaria* described by previous authors and probably due to *Clonorchis infection.*

Increase of periportal tissue in varying degree was observed, as was infiltration with eosinophils. Fatty changes of the liver cells, frequently connected with atrophy of the liver cells in the center of lobules, was found in about one-third of the cases. In 5 cases, the central veins were surrounded by newly-formed fibrous tissue, and in 4 cases there occurred a thickening of the intima in the wall of small arteries and hyalinization of the intima. The results seemed to show that probably in many cases with mild *Clonorchis* infection in which the clinical symptoms are slight or non-existent, already considerable histological changes may be present in the liver.

FIG. 346.—*Clonorchis sinensis* (Jefferys and Maxwell.)

The extent to which the liver is damaged depends upon the number of parasites present and whether there has been continuous reinfection over a period of years, also the length of time the infection has existed. In severe cases, many thousands of parasites have been found and general cirrhosis of the liver has occurred. Sambuc and Baujean reported the finding of 21,000 parasites at one autopsy. In some instances the parasites have been found occluding the biliary ducts, and they have even been found in the pancreatic ducts and duodenum. Hoeppli reports that in some instances it has produced carcinomatous lesions.

Infection of the pancreas is not by any means rare. Katsurada found it in 11.8 per cent of cases of infection. Galliard (1938) has reported 2 cases, both of which complained of acute abdominal pain, oedema, and one of diarrhoea and the other of jaundice. General asthenia progressed and both died. The parasites and notable pathological changes were found in the pancreas. Dilatation of the ducts, atrophy of the gland tissue, proliferation of the epithelium, and inflammatory reactions with local eosinophilia were noted.

Uyeno (1934) has emphasized the pathological changes in the kidney which occur in experimentally infected rabbits. He believes these changes are due partly to the metabolic products of the parasites which are circulating in the blood, and partly to intermediate metabolic products originating from the pathological changes in the infected liver.

Clinical Manifestations.—Many cases of *Clonorchis sinensis* infection of mild type present no unfavorable symptoms. Thus Shattuck found that none of the cases observed at the immigration station in Boston and subsequently in the hospital showed any signs of disease other than a slight eosinophilia. This, while pretty constant, might have been due to the coincident presence of other intestinal parasites which were found in all the cases of clonorchiasis observed. When the infection is severe, the liver may eventually become enlarged and finally sclerotic and there may be chronic diarrhoea, also anasarca and general cachexia may supervene, which may result fatally.

Inouye has particularly studied the disease clinically in Japan. He recognizes (1) a mild type without appreciable symptoms; (2) a stage of severe infection attended by diarrhoea, oedema, and hypertrophy of the liver, and (3) a severe type with symptoms of the second stage, but aggravated by involvement of the hepatoportal circulation due to hepatic cirrhosis. There is no significant modification of the blood picture. Bercovitz has recorded in moderate infections indigestion, epigastric distress, and night blindness as a toxic manifestation.

Diagnosis is made by the discovery of the characteristic eggs in the faeces or in bile or fluid obtained through the duodenal tube.

Prophylaxis.—Infection may be prevented by the thorough cooking of all fresh-water fish intended for consumption. Thorough cooking is essential for protection, as the cysts can survive heating to 50–70°C. for 15 minutes.

In such countries as South China and Indo-China, where fish are killed in the presence of the customer and eaten with condiments in a raw state, dissemination of information regarding the dangers of consuming raw fish, and educational efforts to convey such information, should especially be made to the public in general and through the schools. In such areas, the addition of ammonium sulphate to fresh night soil should be employed as a disinfecting agent.

Tyzzer (1933), emphasizes that whereas *Opisthorchis* may occur frequently in cats in two different countries, it will be found frequently in human beings in the one in which uncooked fish forms an important part of the diet. Where this custom does not prevail, it is confined to animals. Animals and men harboring the parasite should be prevented from fouling water, whether it is used for drinking or bathing or agricultural purposes.

Treatment has been reported as more or less unsatisfactory. Intravenous injections of antimony compounds have been reported as successful in some cases. Chandler states that in the hands of others such treatment has failed. Chopra (1936) states that injections of methyl violet, crystal violet and Nileblue sulphate have been tried and found to be ineffective. He, however, mentions that intravenous injections of 1 per cent solution of gentian violet are said to be very effective. Twenty cubic centimeters are given for the first dose, followed by 30 cubic centimeters 3 days later. Faust recommends genitan violet administered orally in enteric coated tablets, 0.06 gm. 3 times daily before meals for 1 month, and says that it is clonorchicidal provided the dye can reach the worm after it has reached the liver. Kawai, 1937, states that the oral administration of this drug is effective in proportion to the dose administered and the intensity of the infection. In early cases, it is usually curative but in later cases, while it will reduce the number of worms present it probably will not bring about a complete cure.

Otto and Tschan have recommended the intravenous injection of gold salts. In Corea, continuous non-surgical bile drainage by means of the duodenal tube, has been employed for getting rid of toxic material and sometimes by this large numbers of the eggs are removed. It is sometimes necessary to cocainize the throat to prevent reflex vomiting.

Opisthorchis felineus (Risotta, 1884) is normally a parasite in the bile and pancreatic passages of cats, dogs and pigs. The fox, wolverine and seal have also been found infected. The first human case was reported from Tomsk, Siberia. It has been subsequently reported in man, particularly in Siberia and eastern Germany, India, Japan, French Indo-China and the Philippines.

The fluke is about 7–12 mm. long and 2–3 mm. broad. It is lancet-shaped, rounded posteriorly, and attenuated anteriorly. The testes are two-lobed and not dendritic. The ova are yellowish brown with an operculum which fits into the thickened rim of the shell proper. At the posterior end of the shell there is usually a minute tubercular thickening. They measure about 30 by 12μ. The hatching of the eggs does not occur in the water but only after ingestion by certain snails. *Bithynia tentaculata* has been reported as the first intermediate host in which first generation sporocysts and rediae develop. Various fresh water fish (*Idus*, *Cyprinus*, *Barbus*, etc.) may serve as second intermediate hosts. Vogel (1934), has found the snail host in East Prussia to be *B. leachi*, and the principal fish host the tench (*Tinca tinca*).

Symptomatology and Pathology.—The symptoms depend upon the severity of the infection and its duration. In mild cases of infection there may be no unfavorable symptoms and no serious injury done to the liver. In severe infections enlargement of the liver with jaundice has been frequently reported. Cholecystitis and later on formation of bile stones may occur in which the ova serve as nuclei. Inflammatory reactions with deposition of fibrous tissue later may occur around the bile ducts and about the portal vessels, and between the hepatic cells. Plotnikov (1939) has studied the symptoms in 191 cases. He found chronic inflammation of the gall bladder and bile ducts leading to cirrhosis of the liver and chronic pancreatitis as common. Zerchanivov (1939) in a study of the blood of 147 cases in Tobolsk found that in 22 per cent there was anaemia. There was little change in the white cells, except a marked increase in the eosinophils. The clinical picture on the whole resembles that of *Clonorchis sinensis* infection. The diagnosis, prognosis and treatment are similar. However, Szidat and Wigand (1934) state that gentian violet and Fouadin have not been found to be effective for treatment.

Since reservoir hosts exist both in animals as well as man and their excreta may polute the water supply, the sanitary disposal of human faeces alone will not prevent the spread of the infection. Human infection, however, may be avoided in endemic regions by eating only well cooked fish.

Another species of liver fluke, *Opisthorchis viverrini* (Porrier, 1886), is distinguished especially from *O. felineus* by the greater proximity of the ovary and testes, the aggregation of its vitellaria into a few large clusters of granular material, and the different size and shape of its eggs, 26 by 13μ. This parasite has been reported as present in the faeces in about 25 per cent of the natives in the Laos country in northern Siam.

Opisthorchis noverca, (Braun, 1902) a parasite of the dog, has been found in the bile ducts of 2 natives in Calcutta. It is lance-shaped and covered with spines. It measures 10 by 2.5 mm. and the eggs 34 by 21μ, are larger, and hence readily distinguishable from those of the preceding species.

Chandler (1940) points out that the genus *Amphimerus*, distinguished from *Opisthorchis* by having a post-ovarian division of the yolk glands, contains a species, *A. pseudofelineus*, found in cats and coyotes in central United States. It would probably infect man if opportunity were offered. The genus *Metorchis* contains flukes which are shorter and broader than *Opisthorchis*. Cameron (1939) has reported the very common occurrence of a species of this genus, *M. conjunctus*, in many kinds of fish-eating mammals over a large part of Canada. It causes considerable injury to fur-bearing animals, and occasionally occurs in man. The common sucker, *Catostomus commersonii*, is its fish vector. Another representative of this family, *Pseudamphistomum truncatum*, distinguished by the truncated posterior end of the body, inhabits the livers of carnivores in Siberia, and is also likely to occur in man.

The pathogenic effects, treatment, and epidemiology of these infections do not differ in any way, so far as known, from those of *Clonorchis*.

Fascioliasis

Fasciola hepatica (Linnaeus, 1758) giving rise to the disease *Fascioliasis*. Syn. *Distoma hepaticum* (Linnaeus, 1758), *Fasciola californica* (Sinitsin, 1933), *Fasciola halli*, (Sinitsin, 1933).

It was the first trematode to be described by de Brie, 1379, and it was the first digenetic trematode whose complete life cycle was elucidated (Leuckart, 1883, Thomas, 1883).

Geographical Distribution.—*Fasciola hepatica* is normally parasitic in sheep and other herbivorous animals, in which it causes the destructive disease "liver rot." This fluke is cosmopolitan and particularly prevails in sheep raising countries. In the United States, it is endemic in extensive areas in the south and west, as well as in some of the north central states. Practically all herbivorous and a number of omnivorous mammals, including man, have been found infected. The writer (1930) found it in the buffalo, *Bubalus caffer*, in the Ituri forest, Belgian Congo. Over 100 authentic human cases have been reported. According to Faust (1940), in Venezuela, Argentina, Puerto Rico, Cuba, Syria, China, Soviet Russia, France, Italy, Corsica, Hungary, Roumania, Salonica, the Dardanelles, Algeria and French Somaliland.

Morphology.—*Fasciola hepatica* is a fleshy fluke measuring from 25–30 mm. in length by 10–12 mm. in width. It is relatively flat and leaf-like along the margins. Both the intestine and testes are characteristically branched. The two testes lie one behind the other in the second and third quarters of the body. The diameter of the oral sucker is 1 mm., of the acetabulum 1.6 mm. The eggs are ovoidal and operculated, averaging 140 by 80μ. They are laid in the immature stage in the proximal biliary passage of the host and are evacuated in the faeces.

Life History.—The ova mature in water in 9–15 days at the appropriate temperature of 22–25°C. After hatching, the escaping miracidia, which are "eye-spotted," infect various snails a few hours after hatching. Such snails, which serve as the intermediate host, include species of *Lymnaea* (subgenera *Galba*, *Pseudosuccinea*), *Succinea*, *Fossaria*, *Praticolella*, *Bulinus*, and *Ampullaria*. In these snails the parasite develops into first generation sporocysts, then rediae, daughter rediae, and finally cercariae. Mature cercariae, after escaping from the snails, may swim in the water and keep motile for as long as 8 hours.

The cercariae then discard their tails and encyst as minute, white spherules on different forms of aquatic vegetation and on the bark of shrubs, or free in the water. These cysts are viable for a long period when moist, but succumb quickly when dry.

Man and other mammals consuming such vegetation, or drinking at contaminated sites, may contract the infection. The metacercariae excyst in the duodenum and migrate through the intestinal wall into the body cavity. They then pass through the capsule of the liver or via the portal vein and through the liver, parenchyma, to the biliary passages, where they grow to maturity, as demonstrated by Sinitsin, 1915, and Suzuki, 1931. It seems probable that the migrating larvae may also get into the mesenteric veins or lymphatics and eventually be carried to the liver, or in some cases more directly to the right heart, from where they may be carried to unusual localities. Thus Diss (1937) found the parasite in a tumor beneath the mammary gland in a patient 60 years of age. It was formerly thought that the metacercariae might enter the biliary tract directly through the ampulla of Vater. This, however, has not been confirmed by recent investigations.

Pathology.—The symptoms in man are frequently mild. When the infections are very heavy, as in sheep, the passage of the parasites through the liver parenchyma may give rise to mechanical and toxic reactions which may result in necrosis, thickening, and cystic dilatation of the bile ducts, and eventually to portal cirrhosis with cachexia and anaemia. In severe infections, it is not unusual to find small abscess pockets.

In other instances, adenomata of the biliary epithelium may form and areas of eosinophilic and leucocytic infiltration may be found in the liver.

Symptoms.—The incubation period may require 3–4 months from the time of infection. Brumpt and Lavier (1939) report that the early symptoms of infection, before the ova appear and while the larval fluke is establishing itself in the liver, may consist of fever and a very painful liver, sometimes with evidences of pulmonary disturbances at the base of the right lung, together with symptoms of toxaemia. These symptoms often disappear after the flukes have matured and become located in the bile passages. Inflammation of the bile ducts occurs later and the eggs are then present in the faeces. Kouri, who studied 35 cases in Cuba, reported serious symptoms in many, relating to the liver, gall bladder, alimentary canal, and nervous system. In Syria an infection known as "halzoun" (on account of the symptoms of suffocation) has been reported following the eating of raw liver of goats and sheep at sacrificial ceremonies. The parasites attach themselves to the membrane of the throat and mouth, and in some instances wander into the larynx, and give rise to irritation, congestion, ringing of the ears, labored breathing, and at times alarming symptoms, probably of anaphylactic nature.

Flury and Leeb have demonstrated that the toxaemia which occurs in some instances is due to the by-products of the worms and that these may result in the production of a condition of "cachexia aquosa" (Griesinger's disease).

In other cases of human infection, hepatic colic, general abdominal rigidity with pain on pressure, intermittent diarrhoea, urticaria with leucocytosis and eosinophilia, and irregular fever, have been reported. At least several cases have been operated upon for cholecystitis. Croste reported a case in France in which the patient suffered from anorexia, digestive disturbances and diarrhoea, and an incision was made over the liver and into the bile duct for biliary obstruction. The parasites were demonstrated in material from the duct. Leveret and Champagne refer to 3 cases in Algeria, in one of which the parasites were found and the diagnosis made at an operation on the bile duct. In isolated instances the parasites have been found in unusual locations, including blood vessels, lungs, subcutaneous tissues, ventricles of the brain and other organs.

Epidemiology.—Human infection may result from the ingestion of the encysted metacercariae attached to green vegetables. Chandler (1940) notes that watercress is one of the commonest means of infection, but domestic grown watercress is seldom exposed to cercariae of *Fasciola*. The eating of infected raw liver of goats and sheep has proved to be another source of infection. Especially sheep, but also goats, may play an important part in the dissemination of the infection in nature.

Diagnosis.—Diagnosis is made by the discovery of the ova in the patient's stools or from material obtained from the duodenum or biliary tract. Precipitation and complement fixation tests have been recommended as aids to diagnosis, but they have not apparently been extensively employed. In connection with the finding of ova in the faeces in patients who have been eating raw liver, as for example in the treatment of anaemia, it should be noted that false fascioliasis may occur through simple passage of the eggs through the intestinal tract, without resulting infection. Such a condition may be differentiated from actual infection by withdrawing the liver diet for a few days and if the ova continue to be passed the infection is probably genuine.

Prognosis.—Prognosis depends especially upon the severity of the infection. It is usually good or fair in mild infections, but grave in heavy ones, and when serious involvement of the liver has occurred.

Treatment.—According to Kouri* (1932) emetin hydrochloride is valuable. He has administered the drug intramuscularly, 0.03 gm. daily, for 17–18 days. Monnig (1934)

* Kouri (1944) in studies in Havana again confirms the value of this treatment.

has found carbon tetrachloride valuable for removal of the adult parasites, but it is very toxic. Faust reports that tetrachlorethylene is not specific. Montgomery and others, in treating the infection in sheep, have demonstrated that oleoresin of male fern destroys the mature parasites in the bile tracts but does not kill or injure the immature worms passing through the liver parenchyma. Liviere (1934) has advocated intravenous injections of 1 per cent magdala rose dye for human cases.

Prophylaxis.—Pharyngeal fascioliasis may be avoided by the thorough cooking of the infected livers and by avoiding eating raw liver. Also, in infected endemic regions watercress should be avoided. Brumpt and Lavier (1939) who collected 89 cases of human infection, believe that man especially gets his infection from eating raw watercress growing in places to which sheep have access. However, this vegetable may be safe for consumption in districts which are chemically manured and from which sheep are excluded.

Danger of human infection with the parasite will obviously be lessened by detection and eradication of the reservoir hosts, especially infested sheep and goats. Animals should be treated by chemotherapeusis and an attempt should be made to destroy the molluscan hosts either by the use of 1:50,000 solution of copper sulphate or through drainage of pastures.

A closely related but larger parasite, *F. gigantica,* which is more lanceolate and has larger eggs, is a common bovine parasite in Africa and in parts of the Far East. Three cases of human infection have been reported.

Dicrocoelium dendriticum (Rudolphi, 1818), (*Fasciola dendriticum*, Rudolphi, 1819; *D. lanceolatum*, Desjardin, 1845), also a common parasite of the biliary passages of cattle and sheep has been reported in man occasionally. Genuine human infections are apparently relatively few in Europe, Egypt, northern Africa, the Belgian Congo, Java and China. However, extensive parasitic surveys in Russia, Syria, and Shansi Province, China, have demonstrated a number of cases in which the ova of the parasite were found in the stools. Many cases have been reported recently from Tashkent in Turkestan. However, in the majority of the cases in some localities, the presence of the ova in the stools was accounted for by the individuals having eaten more or less raw infected liver of sheep or goats and in which the parasite had not definitely infected the individual and invaded the tissues. It is regarded by some as usually only an accidental infestation of man. Thus Nitzulesco (1939) found ova of *Dicrocoelium dendriticum* present in 3.74 per cent of a thousand examinations. He thinks they were eggs swallowed in food and they were not found when a second examination could be made. In other cases Faust states they were undoubtedly genuine infections as determined by controlled diets.

When the parasites invade the biliary passages in man and animals, similar disturbances to those produced by *Fasciola* may occur. The liver may show small, whitish areas several millimeters in diameter and occasionally small infarctions in which the trematodes are encountered. On histological study, the bile ducts are distended in size and contain sections of the trematodes with ova. The epithelium lining the ducts may be compressed and degenerated or destroyed and there may be infiltrations of round cells and leucocytes about the walls. Often there is an increase in the connective tissues surrounding the bile ducts, the cirrhosis gradually extending outward. Frequently there is more or less necrosis about the parasites and extensive infiltration of the tissue with polymorphonuclear and endothelial leucocytes. In man, symptoms of diarrheoea, dyspepsia, vomiting and enlarged liver have been observed.

The fluke is lancet-shaped, flat, and from 5–12 mm. long and 1.5–2.5 broad and is characterized by having slightly lobed testes anterior to the ovary just behind the ventral sucker. The ova have a thick shell and are golden-brown in color. They are

distinctly operculated, measuring 38–45μ long by 22–30μ. When passed in the faeces they are fully embryonated. They are quite resistant to desiccation and do not hatch in water. After ingestion by appropriate land snails, species of *Zebrina*, *Hellicella*, *Torguilla* and probably other species, cercariae are eventually produced. Cameron (1931) found that when sheep ate the infected snails they acquired *Dicrocoelium* infection.

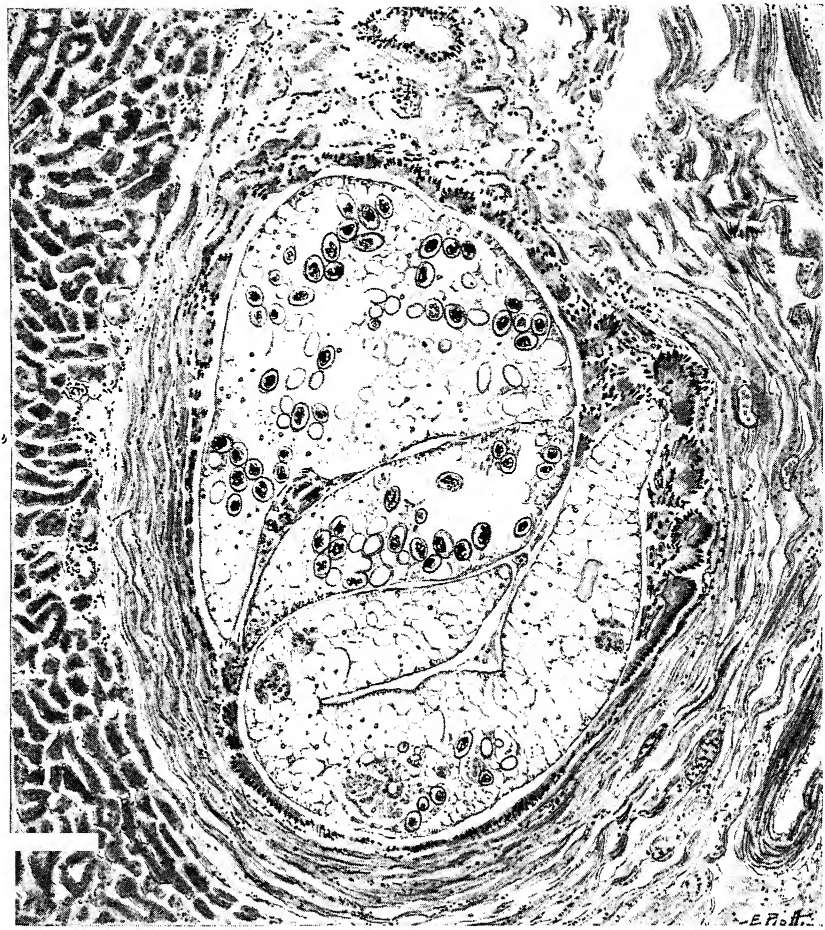

Fig. 347.—Parasites within distended bile ducts compressing and destroying the epithelium. The duct enclosed partially in fibrous tissue. Drawing of section of liver of monkey, illustrating infection with Dicrocoelium colobusicola. (Harvard Liberia Report.)

However, Brown (1933) believes that natural infection involves a second intermediate host, probably a dipterous larva, the imago, of which is eaten accidentally by the definitive host. Neuhaus (1938) has found that the cercariae may invade the respiratory chamber of the snail where several hundred may become enclosed in slimy cysts. These cysts, or slime balls, are dropped by the snail on moist vegetation and after their ingestion by a suitable host the cercariae reach the liver by the portal blood system and are unusual in not losing their tails or stilets until they have reached their final destination.

Chandler reports that another fluke of the same family, *Eurytrema pancreaticum*, lives in the pancreatic ducts of pigs and in the biliary ducts of cattle, water buffaloes, and camels in China. Its thicker body and large oral sucker suffice to distinguish it from *Dicrocoelium*. A few human cases have been recorded from South China.

Treatment for these infections should be the same as outlined for *Fasciola hepatica*.

Intestinal Flukes

Fasciolopsis buski (Lankaster, 1857). Syn. (*Distomum crassum*, Busk, 1859) normally a parasite of the pig, occurs in man quite fre-

Fig. 348.—Degenerated *Dicrocoelium;* infiltration and necrosis of liver tissue. Zeiss objective AA, ocular 4. (Harvard Liberia Report.)

quently in India, China, and Cochin China, and other parts of the Orient.

It is the largest trematode found in man, being a flat, rather fleshy fluke measuring about 40 mm. to 70 mm. long and 12 mm. broad. It is thick, brown in color, and has a very large acetabulum three to four times the size of the oral sucker and located almost adjacent to it. The branched ovary and shell gland lie in the center, with the dichotomously branched testes posterior. The coiled uterus is anterior to the testes. This species is characterized by a very long prominent cirrus. The eggs measure 80 by 130μ, are nearly colorless and have a thin shell and a small operculum. They are passed unsegmented. From two to three weeks are required for the development of the miracidium and about seven weeks more for the development of the cercariae in the snail

(various species of *Planorbis* and *Segmentina*). The cercariae require no second intermediate host but encyst on various fresh water plants, especially the water chestnut, *Eliocharis tuberosa*, and the red caltrop, *Trapa natans*, which convey the infection to man if eaten raw. These are extensively cultivated in ponds in the endemic areas where they are frequently fertilized by throwing fresh night soil into the water. Snails abound in these warm, stagnant pools and the cysts of the parasites are often very numerous upon the stems and leaves of the plants. The snails become infected by miracidia from the ova and the escaping cercariae subsequently encyst on the plants or nuts. The nuts are eaten both fresh and dry. Chandler points out that when fresh they are kept moist and are peeled with the teeth and in this way the cysts gain access to the mouth and are swallowed. Barlow, who examined nuts from the typical ponds, found from a few to over 200 cysts on each nut. Chandler has also traced some cases of infection in eastern Bengal to the water nut, *Trapa bicornis*, closely related to the Chinese nut.

Symptoms.—The parasite inhabits the small intestine, and if numerous may cause diarrhoea, anaemia, and even anasarca and fatal cachexia. While the parasites are usually attached to the duodenal or jejunal wall they are sometimes present in the mucosa of the pylorus. In other instances they have been found attached to the wall of the large intestine. At the point of attachment a local center of inflamation may occur which

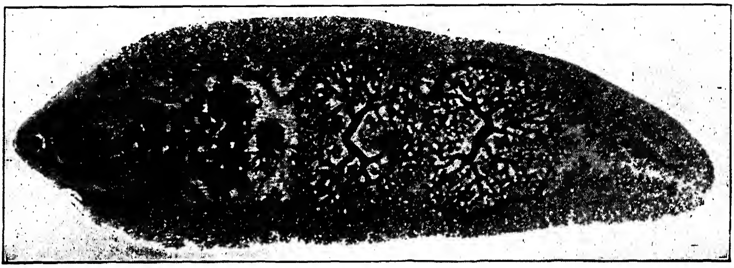

FIG. 349.—*Fasciolopsis buski.* Cleared in glycerin. (From Jefferys and Maxwell.)

usually later results in ulceration. In some instances the capillaries become eroded and haemorrhage results. Abscesses may also develop in the mucosa. The first symptoms are usually a toxic diarrhoea, sometimes accompanied by pain in the abdomen. In mild infection these may be the only notable symptoms. Severe infections, however, may be accompanied by toxic symptoms and the presence of areas of oedema, especially about the face, abdominal wall and lower extremities. Ascites is common and often accompanied by generalized abdominal pain. In advanced stages of the disease, anorexia, nausea and vomiting occur. Later the skin becomes dry and prostration may be extreme. Young (1935) found that nearly half of the cases showed a leucocytosis with an absolute eosinophilia with a neutrophilic leucopenia. At times there was a lymphocytosis. Death has been thought to be due in some instances to the toxaemia following anasarca.

Diagnosis.—The diagnosis may be made by the discovery of the eggs in the faeces. It is practically impossible to distinguish the ova of *Fasciolopsis* from those of *Fasciola hepatica*. However, Kamisaka reports that the yolk granules in *F. buski* are equally

distributed throughout the yolk cells while those in *F. hepatica* are clumped around the yolk cell nuclei. The eggs are operculate and immature when deposited.

Treatment.—McCoy and Chu (1937) have employed hexylresorcinol crystoids (caprokol) in doses of 0.4 gm. for children 1 to 7 years of age, up to 1 gm. for those 13 years or over; 229 cases were thus treated and 54 per cent were cured. In 23 per cent of the cases the egg output was very greatly reduced. It is emphasized that great care must be used to prevent fatalities due to therapeutic agents employed, especially from cardiac failure. Barlow, in earlier years, recommended among other drugs beta-naphthol and carbon tetrachloride. He thinks caprokol is probably superior for treatment.

Prophylaxis.—Vegetables or salads should be immersed in boiling water for a few seconds before being eaten. Copper sulphate, 1:50,000, may be employed for the destruction of the intermediate hosts in the infected areas. Sterilization of the faeces

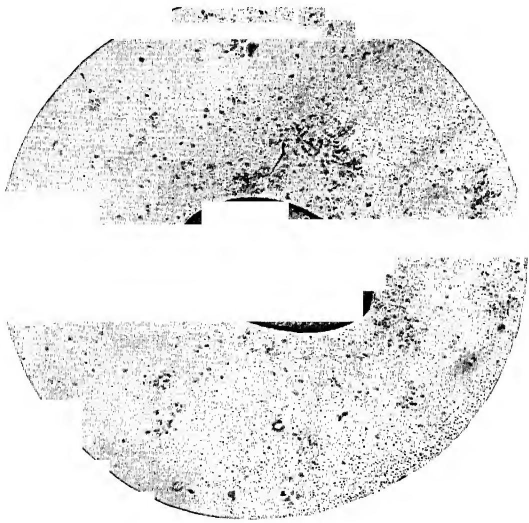

FIG. 350.—Ovum of *Fasciolopsis buski*. (After Bell and Sutton.)

should be carried out whenever practicable. The disease is especially spread in China by means of human night soil for fertilization.

HETEROPHYIASIS

Heterophyes heterophyes (Siebold, 1852), (Syn. *Cotylogonimus heterophyes* Luhe, 1899), This minute fluke was first discovered in the intestines by Bilharz in 1851 at an autopsy of an individual in Cairo. The parasite is common in Egypt in the Nile delta. It has also been found in Palestine and in the Far East, especially in central and south China, Japan and Korea, Formosa and the Philippine Islands. Normally it is a parasite of dogs and cats and the fox, but also occurs frequently in man. The parasite is very small, measuring 1.7 m. in length by 0.3 to 0.4 mm. in breadth. It can be recognized by the large, prominent acetabulum. The oral sucker is much smaller. Very characteristic of the genus is the large, sucker-like genital pore, just below and to one side of the acetabulum and surrounded by a collar of spines. The elliptical testes lie at the extreme posterior end. The cuticle has scale-like spines. The eggs are minute, operculate, light brown, 30–17μ, have a thick shell and contain a developed miracidium when deposited. They hatch only after ingestion by the appropriate fresh water snail. Khalil has reported that the snail *Pironella conica* serves as the first intermediate host in Egypt. Man acquires the infection by eating raw mullet, as *Mugil cephalus*, the second intermediate host, and other species in the Far East.

Symptomatology and Pathology.—The parasites inhabit the ileum, often in large numbers, where they become attached to the wall of the small intestines. At times they are deeply lodged in the crypts. When present in large numbers, they may produce a mild irritation accompanied by colicky pain and mucus diarrhoea. Khalil (1934) has noted that there may be a superficial necrosis of the mucosa and an excess of mucus in the stools.

Africa and his associates, deLeon and Garcia (1940) have emphasized the visceral complications that may occur in connection with intestinal heterophyiasis of man. They have shown that several other species of heterophyids which are apparently not well adapted to man as a host may live in the walls of the intestine and that the ova of these worms may pass through the intestinal wall into the mesenteric lymphatics and become distributed in different parts of the human body where they may cause serious injury. Most frequently lesions were found in the heart, where the eggs were frequently deposited in large numbers in the cardiac valves and myocardium. Here they give rise to symptoms of acute dilatation and a dropsical condition and symptoms similar to cardiac beri beri. The cases often resulted fatally.

In 297 necropsies in Manila, intestinal heterophyid infection was found in 24 and nearly half of these had visceral complications, usually of the heart. In 13, cardiac symptoms were observed in life and the patients were believed to have died from heart failure. The eggs were also found in the brain and spinal cord and have been associated with gross nervous symptoms and with fatal cerebral hemorrhage. Diarrhoea was a very frequent symptom of severe infection. The parasites were found twice in the liver, once in the lungs, and once in the spleen.

The species of heterophids causing these conditions are classified in a number of different genera. Heterophyiasis is primarily an intestinal infection, but in Manila about 44 per cent of the intestinal infections showed visceral complications. Africa emphasizes that the lesions due to the ova of this parasite partake of the nature of a typical reticulo-endothelial proliferation with very little or none at all of the other cellular elements found in other helminth infections.

Diagnosis.—The diagnosis may be made from the discovery of the eggs in the faeces (see above). They somewhat resemble those of *Clonorchis sinensis*.

The *prognosis* depends upon the extent and nature of the visceral invasions with the ova. When the ova are deposited in the heart, cardiac failure and death may occur.

For *treatment*, tetrachlorethylene as prescribed for hookworm infection is recommended.

Prevention depends upon avoiding eating raw or partially cooked or salted mullet or other infected fresh or salt water fish in which the cercariae may develop.

Metagonimus yokogawi Katsurada, 1912 (Syn. *Loxotrema ovatum*, Kobayashi, 1912). This worm was first described by Katsurada as a species of *Heterophyes*. It is probably one of the most common Heterophyidae in the Far East, in Japan, Korea, Formosa, and the Maritime Provinces of Soviet Russia, the northern provinces of Siberia, and the Balkan States. It has also been reported from man in Spain. It is found in cats, dogs and pigs, as well as man. It usually causes very few symptoms. In severe infections, symptoms and visceral lesions similar to those produced by *Heterophyes* occur. However, Africa (1937) states that once the worms invade the mucosa they remain there until they die. Failure of the host to encapsulate the parasites may account for the infiltration of the eggs into the circulation and viscera.

It is a minute fluke, 1 to 2 mm. long and 0.6 mm. wide, inhabiting the duodenum. The acetabulum is displaced to one side, together with the common genital pore. The

latter is not surrounded by a collar of spines. The ova are about 33 by 20μ. They are very difficult to distinguish from those of *H. heterophyes*. The intermediate hosts are: (1) snails of the genus *Melania* and (2) the fresh-water fish, *Plectoglossus altivelis*, *Odontobutis obscuris*, *Salmo perryi*, and *Leuciscus hakuensis*, all of which are valuable food fishes. The cercariae often encyst under the scales.

Echinostomiasis

Echinostoma ilocanum (Garrison, 1908) (Syn. *Euparyphium ilocanum*, *Fascioletta ilocana*). Garrison first discovered the ova of this parasite in natives in Manila in 1907 and later recovered 21 adult worms following administration of oleoresin of male fern. Tubangui and Pasco found that the Norway rat may serve as a reservoir of the infection and that the disease was probably restricted to the Ilocano tribe, inhabitants of the Ilocus Sur, a district in the northwestern part of the Island of Luzon, P. I. They demonstrated the life history of the parasite. Chen (1934) found about 13 per cent of the native dogs in Canton infected with this parasite. Brug and Tesch (1937) next reported it from the Paloe district of the Celebes. Sandground and Bonne (1939, 1940) have found it in Batavia.

Etiology.—The parasite, which lives attached to the wall of the small intestine, is reddish gray in appearance and is a small species, measuring from 2.5 to 6.5 mm. in length and 1 to 1.5 mm. in breadth. At the anterior end it is provided with a circumoral disk and has a crown of 51 spines and a spiny body. The oral sucker lies in the center of the oral disk, the ventral sucker in the anterior part of the body proper. There are 2 massive, deeply-lobed testes, one behind the other, in the third quarter of the body, and the transversely ovoidal ovary is situated in front of the anterior testes. The straw-colored, operculated eggs measure 83–116μ by 58–69μ and are immature when passed in the faeces, but mature in water in 6–15 days.

The same or a closely related species, *E. malayanum*, a larger fluke with 43 collar spines, has been found to infect a high percentage of certain of the tribes of the Sino-Tibetan frontier and of the Tamils of the Malay States. Sandground and Bonne (1940) have found a high incidence of human infection with a species they named *E. lindoensis*, which has 37 collar spines and closely resembles the species *E. revolutum* of ducks and other aquatic birds. It was encountered around the shores of Lake Lindoe in the Celebes. It is apparently primarily a human parasite, for natural infections were not found in either rats or water birds.

Life History.—The ova of *E. ilocanum* hatch in water and the miracidia penetrate the viscera of a snail, in Luzon, *Pila luzonica*, according to Tubangui and Pasco. They fed this snail, as well as other snails that harbored the metacercariae, to many laboratory white rats and monkeys and a cat, all of which animals became infected within the course of a few weeks with the adult worms.

According to Rao, in India, *E. malayanum* invades the snail, *Lymnaea luteola*, as the first intermediate host, while a fish, the Barbel (*Barbus stigma*) as well as the snail, may serve as the second intermediate host.

Sandground, working in Batavia, has found the developmental stages (metacercaria) of *E. ilocanum* present in a large proportion of the Planorbid snails, *Anisus convexiusculus*, Hutt, and later also in *Lymnaea rubiginosa brevis* Mous., *Viviparus javanicus* Phil., and *Pila conica* Gray, the species of snails being identified by Bequaert (1940). Laboratory raised white rats were experimentally fed with the above named infected snails and became infected with *E. ilocanum*. A transient human infection was obtained by the ingestion of metacercariae from the snail *Anisus*.

With *E. lindoensis*, in a small planorbid snail, *Anisus sarasinorcum*, larval development was found in natural infections. The metacercariae were found in several pulmonate snails, *Viviparus javanicus rudipellis*, and also in the mussel, *Corbicula lindoensis* Boll. These mussels form a regular part of the diet of natives.

Symptoms.—Bonne (1940) describes the symptoms in the main as diarrhoea and slight pain in the bowels. In experimental human infec-

wall, the ova may give rise to a diarrhoea, with the presence of ova in the stools. In the skin and subcutaneous tissue, abscesses sometimes develop. Musgrave found some hundred mature parasites in a psoas

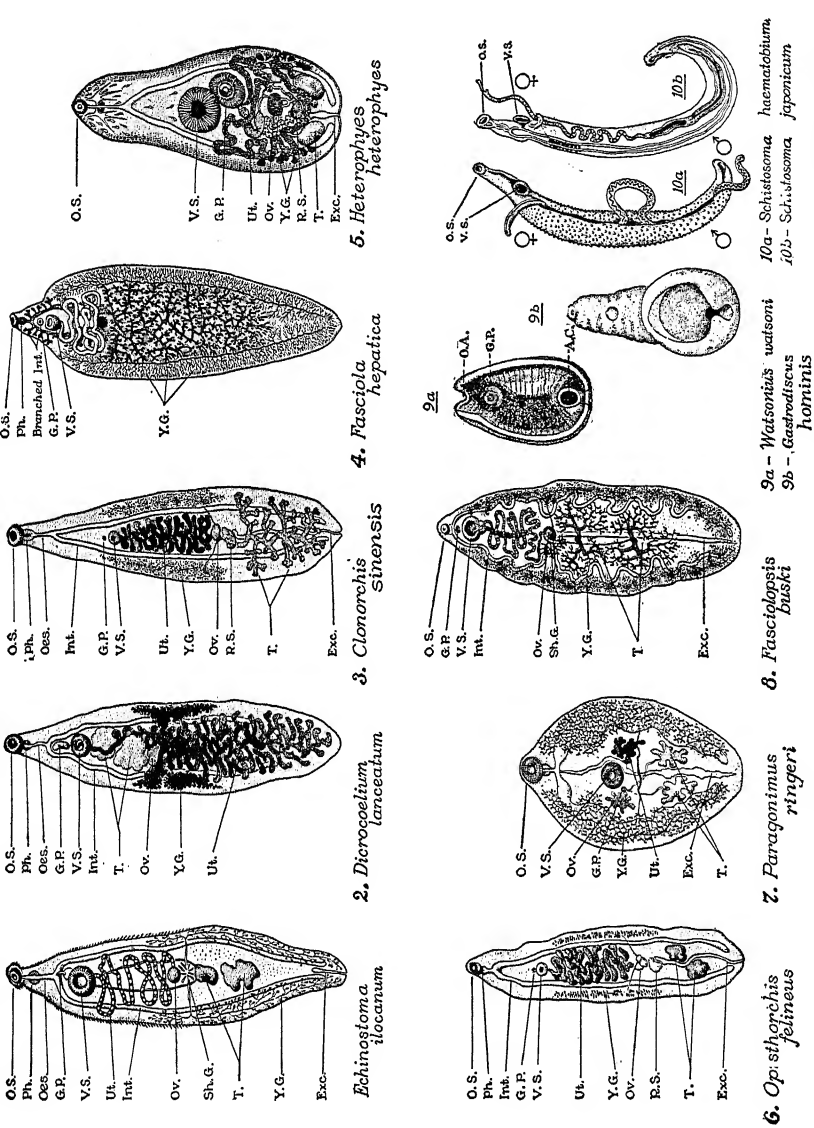

Fig. 353.—Anatomy of trematoda (flukes) of man, *O. S.*, oesophageal sucker; *Ph*, Pharynx; *Oes*, oesophagus; *G. P.* genital pore *V. S.*, ventral sucker or acetabulum; *Ut.*, uterus; *Int.*, intestines; *Ov*, ovary; *Sh.G.*, shell gland; *T.*, testicles *T.G.*, yolk glands or vitellari; *Exc.*, excretory pore. Not drawn to scale.

abscess. Ko (1939) also found large numbers of ova in a discharge from an abscess in the left side of the lower abdomen, as well as in the sputum. In some instances there is glandular involvement which may be accompanied by fever. Jacksonian epilepsy has been reported as occurring in

paragonimiasis, the ova being found in cysts of the brain. There is some question as to whether some of the earlier reports as to cerebral paragonimiasis may not have been connected with infections with Japanese schistosomiasis. However, in Japan a number of cases in children, with brain symptoms attributed to infantile paralysis, encephalitis, meningitis, or cerebral haemorrhage, were subsequently found to be due to infection with *Paragonimus*.

Diagnosis.—The diagnosis of endemic haemoptysis is readily made by finding the operculated eggs in the more or less sanguinolent sputum. The sputum also usually contains altered blood corpuscles and eosinophiles. Charcot-Leyden crystals are often present. The faeces also should be examined. Eggs that are swallowed with the sputum may be found in the faeces even in the absence of intestinal lesions. Ando has described a Bordet-Gengou complement deflection test, using an extract of the adult worm as antigen as an aid to diagnosis in obscure cases of the abdominal and cerebral type.

Prophylaxis.—The first step in prevention is to avoid the eating of raw or partially cooked crabs or crayfish. There is also a possibility that the cysts on the gills of the crustaceans may escape into the water and on drinking this water man may become infected. Chandler has recommended the treatment of water supplies with 1 to 1,000,000 copper sulphate which will kill the mollusks. It also will kill algae, but unfortunately it also may kill the young of some species of fish. The sputum of patients should be sterilized.

Treatment.—Tartar emetic does not seem to have much effect on the fluke, but there have been encouraging reports from the use of emetine. Martin has tried mercurochrome in combination with emetine. Emetine hydrochloride has been especially recommended, and Kobayashi and Ando have reported encouraging results with this drug, which is said to lessen sexual activity of the trematodes. It was injected intramuscularly into patients in doses of 1.25 cc. of a 2 per cent solution, 4 times daily for 5 days, but it must be used with great caution, especially in cases where there is any myocardial trouble.

Bercovitz recommends emetine in 1 gr. daily doses for periods of 7 days. He also reported marked improvement following lipiodol injections into the bronchi.

Yokogawa (1940) has reported good results in the treatment of *Paragonimus* infection by prontosil. Three dogs were first treated successfully with 2.5 per cent solution of prontosil with emetine hydrochloride, which brought about rapid and radical cure. Nine human cases were then treated by intramuscular injections of prontosil, 2.5 per cent, to a total of 60 to 165 cc., and with intravenous emetine hydrochloride 4 per cent to a total of 12 to 23.5 cc. over a period of 7 to 17 days. In 6 patients the treatment was continued until the eggs, after a temporary increase in number during the first 4 days, disappeared from the sputum. In 3 it was stopped when the degenerative changes in the eggs became conspicuous, but in these the eggs finally disappeared. Of the 9 patients, 2

could not be followed; 4 had no recurrence of symptoms 5 months later; 1 died of unrelated disease; and 2 relapsed with much haemoptysis.

Faust (1940) appears to be doubtful about cures resulting from the use of emetine. He recommends removal of the patient from the endemic foci, when the clinical symptoms are usually less severe after 5 or 6 years.

Troglotrema salmincola (Chapin, 1926) are small flukes, 1 mm. or less in length, belonging to the same family as *Paragonimus*. They are common parasites of fish-eating mammals (dog, coyote, fox, raccoon, mink and lynx) in northwestern United States, and of eastern Siberia. Human infection has been reported from eastern Siberia. The snail host in Oregon, U.S.A., according to Donham, Simms and Shaw (1932) is *Goniabasis plicifera*. The free swimming cercariae (from the snail) become attached to and later encyst primarily in the kidneys of the salmon and trout. When eaten uncooked, infection occurs in the definitive host in the small and large intestine, in which the parasite becomes deeply imbedded. The parasite in itself is apparently not associated with the production of disease, but it is of interest because its presence has been associated with a highly fatal disease in dogs called "salmon poisoning." Simms and his associates (1932) have obtained evidence that the disease is caused by a virus for which the fluke serves as a vector. The fluke lives in the intestinal wall of the host.

After an incubation period of a week or more, there is loss of appetite, fever and sensory depression, followed by oedema, violent vomiting, and dysentery. Following the disappearance of these symptoms, the temperature may drop and death ensue within 24 hours to 48 hours. Recovery from one attack confers immunity. If the case is diagnosed within 3 hours of onset, from 2–6 milligrams of apomorphine by mouth is said to protect the animal. However, the severe symptoms caused by the virus have not been described in man. Strom (1935) has reported that aspidium is an efficient anthelmintic for removing the worms from human cases.

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Chapter XLIX

CESTODES

INFECTIONS WITH CESTODES

Although some 25 or 30 different species of tape worm have been reported as attacking man, there are only 4 adult species and 3 larval species which are at all common. Of the family DIPHYLLOBOTHRIIDAE, *Diphyllobothrium latum* as an adult is very common, while the larval form of *D. mansoni* (*Sparganum mansoni*) is much less common. Of the family TAENIIDAE, as adults *T. solium, T. saginata;* and *Hymenolepis nana*, and as larvae *Taenia solium* (*Cysticercus cellulosae*) and *Echinococcus granulosus* are likewise prevalent. *Hymenolepis diminuta* and *Dipylidium caninum* are fairly common, but all other tape-worm infections are rare in man. *Taenia saginata* and *T. solium* and their larval or cystic forms are frequent in different parts of the tropics and subtropics, while *Hymenolepis nana* is largely limited to, and *Sparganum mansoni* and *S. proliferum* are generally more common in warm countries. *D. latum* is more common in northern climates.

Zoological Considerations.—Anatomically a tape-worm may be considered as a series of individuals united in one ribbon-like colony. It is made up of a relatively minute "head," the ancestral or mother segment, and a series of daughter segments (*proglottides*) which arise from the head by a continuous process of cell proliferation. The head and the adjacent slender portion of the body in which segmentation is not distinct (the "neck") together constitute the *scolex*. The scolex and the proglottides constitute the *strobila*. The head is provided with sucking discs, and frequently with hooklets carried by a protrusible structure, the rostellum, which enable the parasite to attach itself firmly to the intestinal mucosa. These structures are important in classification. The head is the portion of the worm which is of primary importance. The permanent evacuation of one of these parasites is accomplished only when the head as well as the segments is expelled. Otherwise the strobila will be reformed from the head.

The *head* contains the central nervous tissue and the commencement of the water-vascular (excretory) system. There is no digestive system, nourishment being absorbed directly from the intestinal contents of the host.

The *proglottides* may be regarded as sexually complete, hermaphroditic individuals, practically "egg factories." They are covered by an elastic cuticle, and in their interior contain elliptical bodies composed of calcium carbonate, varying from 5 to 25μ in diameter in different species. These calcareous bodies are characteristic of cestode tissue. Aside from the sex organs they contain near each lateral margin, running the entire length of the worm, a slender nerve fibre and a pair of excretory canals which usually communicate with the opposite canals by a transverse canal. The segments vary in number from 4 in the *Echinococcus* to 3000 or more in *Diphyllobothrium latum*. The mature segments are at the caudal end.

Each segment contains a central uterus, often with a varying number of lateral branches, ovaries (near the ventral surface), vitelline glands for the secretion of yolk, a shell gland, and a vagina leading from the genital pore to the receptaculum seminis and

to the oviduct. From the latter a duct runs to the uterus, in which the eggs accumulate. Each egg contains three pairs of hooklets. There are also minute testes, from three to many in the tapeworms of man, a system of collecting tubules and a vas deferens opening at the genital pore, and differentiated at its terminal portion into an intromittent muscular organ, the cirrus. Fertilization of ova may be effected by sperm from the same

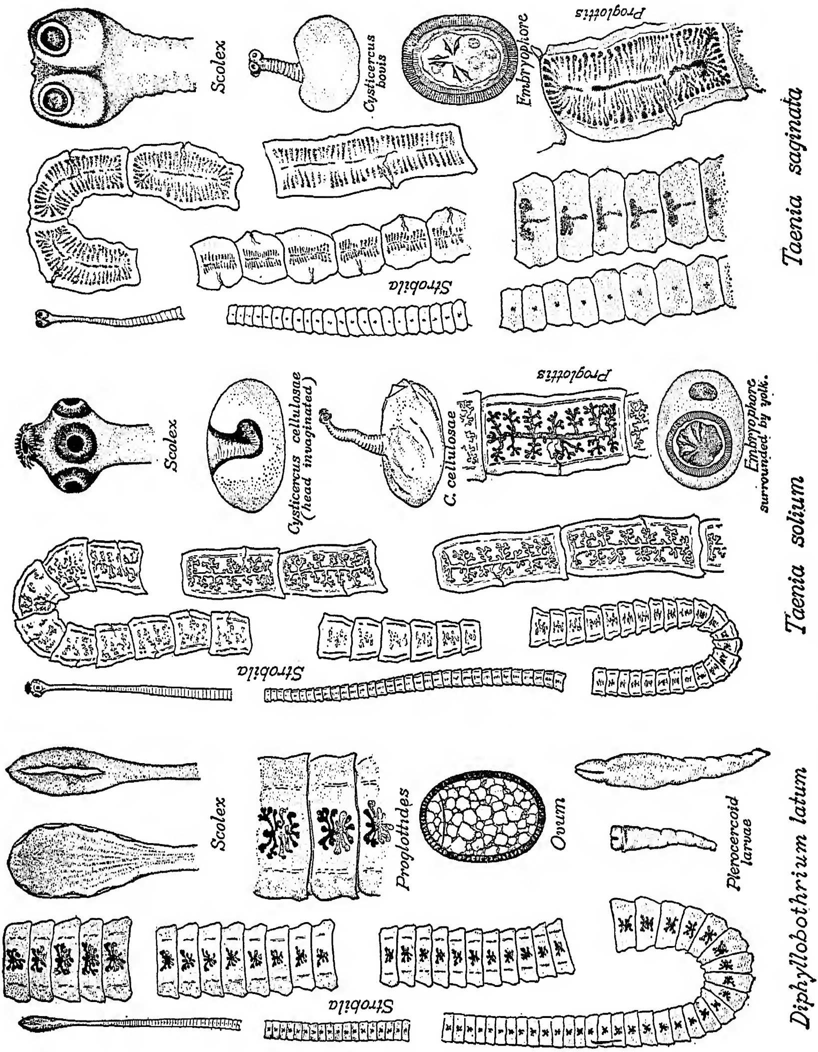


FIG. 354.—Adult and larvae stages of cestoda of man.

segment, or from other segments of the same worm, or of other worms. The eggs are not discharged through the genital pore. In *Diphyllobothrium* the eggs are discharged consecutively through a special birth pore. In *Taenia* there is no birth pore, the uterus ends blindly, and eggs are liberated only after disintegration of the segment. This may occur in the intestine, and then numerous eggs may be found in the faeces. In other cases one or more mature segments may detach themselves and be passed intact in the faeces (which then do not contain eggs). In the case of *Taenia saginata* the segment

may wriggle out through the anus, or if faeces have been deposited on the ground it may creep away from the faecal mass into the grass and there disintegrate and liberate eggs in a situation in which they are likely to be eaten by a cow.

Life Cycle.—Practically all cestodes require both a definitive and an intermediate host. For nearly all species infecting man, *man is the definitive host* and is usually injured little if at all by the infection. The *intermediate host* may be another mammal, a fish or an arthropod. In the TAENIOIDEA, when eggs are swallowed by an appropriate host, the shell is dissolved, and the liberated embryo (onchosphere) with the aid of its hooklets burrows through the gut wall and penetrates into a suitable tissue where it encysts, producing a bladder-like structure containing fluid. The hooklets are then discarded. At one or more points the cells in the wall of the cyst proliferate and invaginate to form a scolex. If a single onchosphere gives rise to a single cyst containing a single scolex, as in Taenia, the structure is called a *cysticercus*. If it produces a single-cyst containing many scolices, it is termed a *coenurus*, as in "*C. cerebralis*" of sheep (the larval form of *Multiceps multiceps* of the dog). If it forms many cysts each containing many scolices, an *echinococcus*. The term *cysticercoid* is applied to a cysticercus which is minute and contains very little fluid, as in *Hymenolepis*. When the cyst is ingested by the definitive host the scolex evaginates, attaches itself to the intestinal wall and develops into the adult worm.

Man is an intermediate host in the case of *Echinococcus granulosus*, rarely of *T. solium* and a few other cestodes, and may suffer serious injury from such infection.

KEY TO IMPORTANT CESTODE SPECIES FOUND IN MAN

I. Head with two elongated slit-like suckers; genital pores ventral; rosette-shaped uterus. Bothriocephaloidea.
  - *A*. Single set of genital organs in each segment. *Diphyllobothrium.*
  - *B*. Double set of genital organs in each segment. *Diplogonoporus.*
  - *C*. Immature forms showing characteristics of Bothriocephaloidea (collective group). *Sparganum.*

II. Head with four cup-like suckers; genital pores lateral. Taenioidea.
  - *A*. Uterus with median stem and a varying number of lateral branches.
    - (1) Head with two rows of hooks. Many segments. Uterus with 5 to 12 lateral branches. *Taenia solium.*
    - (2) Head without hooks. Many segments. Uterus with 15 to 30 lateral branches. *Taenia saginata.*
    - (3) Head with two rows of hooks. 3 to 5 segments only. *Echinococcus granulosus.*
  - *B*. Uterus without median stem and lateral branches.
    - (1) Genital pores single. Rostellum with not more than two rows of hooks.
      - (*a*) Suckers armed with numerous small hooklets. Fifteen to twenty testes in each segment. *Davainea.*
      - (*b*) Suckers not armed. Three testes in each segment. *Hymenolepis.*
        - (1) Rostellum with a single row of hooklets. Length 1 to 8 cm. *Hymenolepis nana.*
        - (2) Rostellum unarmed. Length 20 to 60 cm. *Hymenolepis diminuta.*
    - (2) Genital pores double. Rostellum with four or five rows of hooks. *Dipylid-*

Taeniasis

Taenia saginata (Goeze, 1782), the beef tape-worm or unarmed tapeworm, is found throughout the world wherever beef is eaten. Man is the definitive host, cattle act as intermediate host. It is the commonest large tape worm of man, next to *Hymenolepis nana*, in the United States. It has a world-wide distribution. In some localities, as in Africa and Syria, and also among Tibetans, one-fourth to three-fourths of the inhab-

itants are reported as infected. The Tibetans prepare beef by broiling it in large chunks over an open fire. This sears the surface but scarcely warms the interior. However, in the Hindu sections of India, infection with *T. saginata* is practically unknown among the natives, since only the lowest outcasts will eat meat from the sacred cow, or even that from water buffalo.

Morphology.—The adult worm is found in the proximal part of the small intestine. It is from 4 to 8 meters long and is made up of several hundred (up to 2000) segments. The small pear-shaped head (1.5 mm.) has four pigmented elliptical suckers but no hooklets. The armed rostellum of *T. solium* is absent, being replaced by a depression (sucker). The mature proglottides are plump, about 18 to 20 mm. long and 5 to 7 mm. wide. There is a single genital pore which usually appears on opposite sides of adjacent segments. The uterus has 15 to 30 slender lateral branches on each side which show forking or tree-like branching, in contrast to *T. solium* which shows 5 to 12 lateral divisions only. There are two ovaries.

Life Cycle.—The *eggs* are slightly ovoid, about 25 by 35μ in diameter, and possess a thin transparent outer shell which is usually lost in the faeces. Within this there is a thick, radially striated layer (the embryophore) containing the embryo proper (the onchosphere) usually with three pairs of hooklets. The eggs can not be distinguished with certainty from those of *T. solium.*

After ingestion by the cow the onchosphere is liberated in the small intestine and penetrates into the tissues, especially the diaphragm, heart, tongue and masticatory muscles. Here they become encysted, forming small bladder-like structures about 6 by 8 mm. in size (bladder worms), containing a small scolex but relatively little fluid (*Cysticercus bovis*). The absence of hooklets about the head distinguishes it from *Cysticercus cellulosae* the larva of *T. solium.* They remain quiescent in the muscle but viable for many months at least. All reports of this larval stage in man are open to question.

Infection.—Human infection is acquired from consumption of infected beef containing the *Cysticercus* larvae. When infected meat is eaten raw or inadequately cooked, the cyst wall is dissolved, the scolex attaches itself to the intestinal wall and grows rapidly, reaching the adult stage after about two months. The maximum duration of life is not known but is at least several years. Cattle become infected from grazing on ground which has been polluted by human faeces containing the ova of the parasite. Penfold and Phillips (1937) have reported that the ova may remain viable on exposed pastures for 8 weeks or longer.

Pathology and Symptomatology.—During the later stages of the incubation period, when the parasite is in the intestine and is reaching the adult stage, diarrhoea and hunger pains not infrequently develop and a loss of weight may occur. What is known as the proverbially ravenous tape worm appetite is common. During the early stages of infection a leucocytosis may occur, together with an eosinophilia which in some instances has reached 34 per cent. Later in the disease there is more usually a slight leucopenia. The presence of the parasite in the intestines usually causes no distinct lesions, although mechanical injury may result at times from its obstructing the intestinal canal and slight injuries to the mucous membrane may occur at the point to which the parasites adhere. In a few instances reports of appendiceal colic have been made, in which the proglottides of the worm became clogged in the appendix. The parasites may also cause digestive disturbances and nervous symptoms due to the production of toxic substances which are absorbed.

Swartzwelder (1939) in a study of 60 cases in New Orleans, found abdominal pain, excessive appetite, weakness, and loss of weight to be the commonest symptoms. Other patients may experience nausea, difficult breathing, digestive disturbances, dizziness, restlessness, insomnia, and occasionally convulsions or epileptic fits. Some patients become greatly emaciated.

Chandler (1940) reports a case which had been treated for tuberculosis. The patient was weak and easily exhausted and subject to mental disturbances, his cheeks were sunken, his frame emaciated, and eyes staring. Within a fortnight after 2 large *Taenia* had been expelled, his condition was entirely changed for the better, although he had been suffering for over a year. On the other hand, many cases remain in robust health and reveal almost no symptoms of infection.

Prophylaxis depends upon adequately cooking beef, adequate inspection of all meat and sanitary disposal of human faeces. The parasites are easily killed by heat. They are also killed by thorough salting and by refrigeration for three weeks or more. It is probable that the various raw meat cures have made the infection more common.

Abnormalities of both the scolex and the proglottids are common. Several related species which have been described are believed by many to be merely variants of *T saginata* as *T. confusa* in the United States, Nigeria and East Africa (4 cases); *T africana*, E. Africa, (2 cases); and *T. philippina* in Philippines, *T. bremneri*, 1 case in Nigeria, etc. For *treatment* see p. 1472.

Taenia solium (Linnaeus, 1758), the "measly-pork" tape-worm, has a world-wide distribution and may be met with wherever raw pork is eaten. It is very rare in the United States, Canada and England, but is fairly common in north-east Germany and some other parts of Europe, especially among the Slavic peoples. It is not found in Jews, Mohammedans, or other races that do not eat pork. Man is the definitive host, and the hog the normal intermediate host. However, man may serve as intermediate host of the larva, and this form of the infection (*Cysticercus cellulosae*) is commoner, or more often recognized, in man than infection with the adult parasite.

In many parts of the world, as in North America, India and the Philippines, Chandler points out, human infections with adult worms are so rare that many laboratories are unable to obtain specimens of the parasite for instruction, yet bladder worm infection (*Cysticercus*) in pigs is of fairly frequent occurrence. This is yet unexplained. The pig, however, is not the only intermediate host of the parasite. The bladder worms, or cysts, have also been reported in dogs, monkeys, and in camels, as well as in man.

The adult is somewhat smaller than *T. saginata*, rarely exceeding 1000 segments and 2 to 4 meters in length. The head is globular, 1 mm. in diameter, and has a rostellum armed with 26 to 28 hooklets. The mature proglottides are 5 to 6 mm. wide and 10 to 12 mm. long. The uterus shows 5 to 10 or 12 coarse lateral branches. There are two ovaries, but the ovary on the pore side sometimes shows a small section separated from the rest of the ovary by the vagina. The segments are passed with the faeces, but do not migrate spontaneously from the host. The eggs are spherical or slightly oval, measure 30–40μ in diameter, and are buff to walnut in color, with a thick wall radially striated. Within there is a vitelline membrane enclosing the fully developed embryo or onchosphere, with usually 3 pairs of hooklets. According to Yoshino (1934) as many as 9 pairs may be present.

Life Cycle.—When man is infested, segments, single or in chains, are expelled from the intestines almost daily. Frequently several hundred are passed during the month, each segment containing thousands of eggs. Either before or after leaving the body, the proglottides by their own movements frequently rupture the uterus anteriorly and force out most of their ova. Either the ova or the proglottides, which may reach pigs through their water or food, become ingested. Upon ingestion by the pig or other suitable animal the onchospheres or embryos are liberated and then bore through the

intestinal wall and make their way through the blood or lymph channels, usually to the muscles or "meat," often localizing in the tongue, neck and shoulder muscles, but any tissue or organ may be involved. When they arrive at their destination they grow into bladder worms or *Cystercercus cellulosae.* These are small, oval, whitish bodies with an opalescent transparency 6–18 mm. long with a denser white spot on one side where the scolex is invaginated. Such pork is called "measly-pork." Development takes about 3 months, when they attain a diameter of 6–12 mm. They may remain viable in pork for years.

Human infection is acquired when undercooked pork containing the bladder worms is eaten by man. The scolex is then digested and the latter, turning right side out, anchors itself to the wall of the small intestine and grows to maturity in about 2 or 3 months. While considerable growth of this parasite may take place in dogs, man is the only final host so far as is known.

Symptomatology and Pathology.—The adult *Taenia solium* in the intestines gives rise to the same symptoms as described for *Taenia saginata* (see above). In many robust patients, the symptoms are not very disturbing. However, rare cases have been reported in which the scolex had apparently perforated the intestinal wall, giving rise to peritonitis. Also, *T. solium* is particularly dangerous because the larvae, or bladder worms, as well as the adult, can develop in man. Thus if the eggs are ingested by man, or if self infection with the eggs results (either from contaminated hands or by ripe segments of the parasite being carried back to the stomach by reverse peristalsis), the embryos may be liberated there by the action of the gastric juice and after migration into the somatic or visceral organs give rise to cysticercosis. In such cases, any organ of the human body may become infected, including frequently the brain and occasionally the eye. In such localities the cysts may become quite large and cause grave disturbances. It is, therefore, very important to identify the adult parasite when present, to enforce rigorous precautions to avoid ingesting eggs, and to institute treatment promptly.

Clinical and Pathological Features.—The effects produced by the *Cystercerci* in man depend upon the severity of the infection and the location in the body. A few, when situated in the muscles or subcutaneous connective tissue, may cause little disturbance. However, when the parasites locate in the eye, heart, spinal cord, or brain, they may give rise to alarming or serious symptoms, especially as a result of mechanical pressure. They have been found most frequently in the subcutaneous tissues, but infection of the brain is very frequent, where they have been encountered commonly in the ventricles or in superficial cysts and may give rise to convulsions, epileptic attacks and paralysis. Next to the brain in order or frequency, they have been found in the eye, the muscles, heart, liver, lungs, and abdominal cavity.

The presence of the growing larvae in the tissues usually gives rise to a local inflammatory reaction and infiltration of the area with lymphocytes, neutrophiles, eosinophiles and plasma cells. Later the *Cysticercus* becomes surrounded by a fibrous capsule. Giant cells may appear. In other instances necrosis may occur and be followed by caseation or calcification of the larvae. The calcified cysts act as foreign bodies in the brain.

Clinically the infection in the brain is a common cause of convulsions and epileptic attacks. Such attacks and their common occurrence have in recent years been emphasized particularly by MacArthur (1934) Dixon and Smithers (1934) and Chung and Lee (1935). MacArthur has shown that the frequency of epilepsy in the British Army,

especially in soldiers who have served abroad, is due to cysticercosis of the brain. In some instances, cerebral tumors had been suspected before correct diagnosis of cysticercosis was made. Nervous symptoms other than fits may occur, and the initial symptoms may resemble disseminated sclerosis. Psychical states have been reported, with cerebral irritability or loss of memory. Even acute mania or melancholia has been observed.

Diagnosis of the intestinal infection with worms of this genus can sometimes be made by finding eggs in the faeces, but the species cannot be identified in this way. Precise diagnosis depends upon finding and examining a segment of the worm. This should be mounted between 2 slides and compressed sufficiently to make clear the lateral branches of the uterus, when differentiation can be made by counting the main lateral arms of the uterus, 7–13 on each side as distinguished from 15–20 for *T. saginata*. After an anthelmintic, all the stool should be saved and screened and the sediment thoroughly searched for the head, using a hand lens. If the scolex is found, the armed rostellum differentiates the parasite from *T. saginata*. If the head is left behind, a new worm will develop, but 2 or 3 months may elapse before eggs or segments reappear. There may be several worms present.

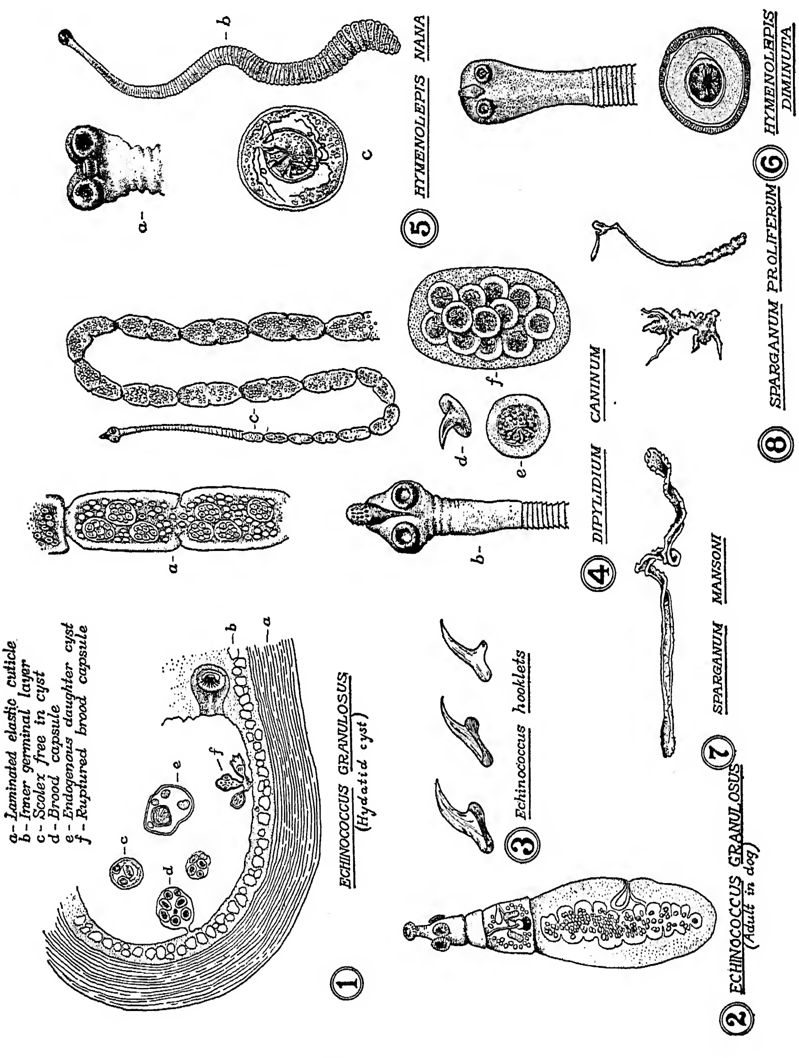
Diagnosis of Cysticercosis.—In cases of epileptic attacks or similar nervous symptoms, a careful search by palpation should be made to discover any cysts. They may be the size of a small pea, a hazel nut, or even a pigeon's egg. Their distribution varies. They have been found in the lips, masseter muscles, in the tissues of the neck, chest, abdominal wall, back and groin. If they are not numerous, they may easily be overlooked. At the time of examination they may be absent, but appear at a later date. Radiological examination may not reveal them, as calcification usually does not occur before several years after infestation. If cysts are demonstrated, they should be excised whole under novocain anesthesia and the entire host capsule removed, care being taken not to injure the cysticercus. When the parasite becomes calcified, a good skiagram will frequently reveal it as a small, elongated shadow. Manson-Bahr reports that evidence of calcification within the brain has been demonstrated in 5 cases. Unfortunately the eosinophile count is no aid to diagnosis, as in no cases so far investigated has an increase been shown. Complement fixation tests have also not been of great value, since in some instances a negative test does not exclude the infection and the intradermal Casoni test was positive in only about half the cases.

There have been several fatal cases in which the cysts were found at autopsy limited to the brain. No constant changes have been found in the cerebro-spinal fluid. Sometimes the epileptic seizures cease without apparent cause. In other cases they have persisted for 8 years or more.

Prophylaxis.—Since consumption of raw pork may expose the individual to infection with the pork tape-worm, as well as to trichinosis, insufficiently cooked pork should be carefully avoided. Public instruction should be given, especially in the schools, of the danger of faecal contamination which makes it possible for man to acquire cysticercosis either from himself or from others infected with the adult worms. Sanitary laws should be enforced regarding the disposal of human excreta in endemic foci and rigid inspection of pork in all slaughter houses carried out and condemnation and destruction of "measly pork."

With reference to the destruction of cysticerci in pork, the parasite is killed when heated to 55°C., but the difficulty of heating the center

of a large piece of meat even to this point is shown by the fact that in an experiment made to test the penetration of heat, a ham cooked by boiling for 2 hours had reached a temperature of only 46°C. in the center. It is advised that when there is any question of infection the pork to be roasted



should be cut into pieces weighing no more than 3 or 4 pounds to insure thorough penetration of heat. Pickled and salted pork are not necessarily safe.

It is commonly believed that human cysticercosis is an accidental complication, occurring in the host with an adult tapeworm, the autoinfection being caused by the ingestion of eggs, or possibly by regurgita-

tion of segments into the stomach. Manson-Bahr (1940) believes it is much more probable that the infecting eggs are conveyed from some extraneous source, and it is possible that the infection is acquired in some

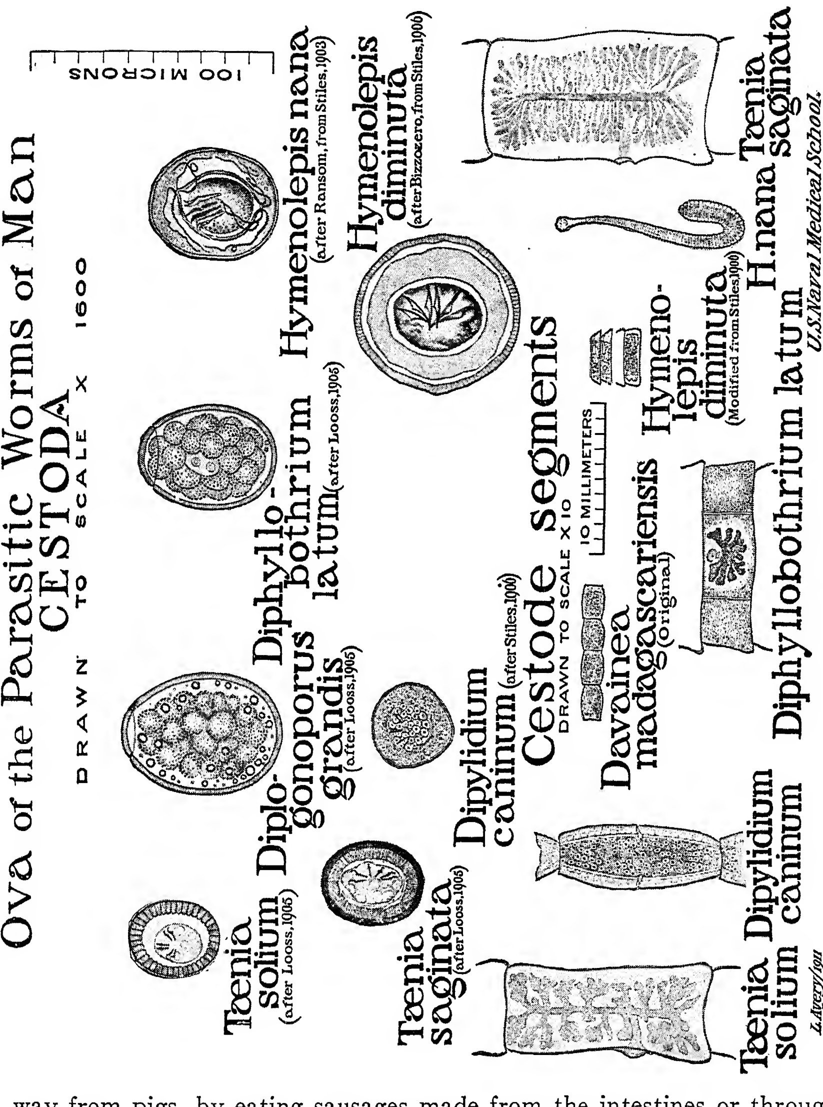


FIG. 356.—Cestode ova and segments.

way from pigs, by eating sausages made from the intestines or through some contamination by pigs excreta. (For treatment see p. 1472.)

Hymenolepis Nana (Siebold, 1852), (Taenia Nana).—The family Hymenolepididae contains a large number of species of tape-worms parasitic in birds and mammals. Three species have been found in man; *Hymenolepis nana*, which is very common in both man and rats and

mice; *H. diminuta* is abundant in rats and mice and fairly common in man; and *H. lanceolata* (*Drepanidotaenia lanceolata*), a parasite of dogs and geese which has been reported in man only once and the infection may have been accidental.

H. nana, the dwarf tape-worm, is the smallest of the human tape-worms and the commonest in the United States. It has a world-wide distribution, but is, of course, commoner in some localities than others and is particularly encountered in warm countries.

Stiles found it in 5 per cent of the children of a Washington (U. S.) orphanage, and it is estimated that about 1–2 per cent of the population, especially children, are infected in the southern United States. Sunkes and Sellers (1937) in a study of data from faecal examinations in the southern states, obtained records of 8085 tape-worm infections: 98.6 per cent were *H. nana*. It is also common in Brazil and Argentina, Egypt, the Sudan, Siam, and Japan. Apparently it is less common in parts of China. Wang (1938), in Peiping, found it in 0.33 per cent. Chandler, (1940) found in some parts of India as high as 18.28 per cent of the population infected. It is found throughout Europe, but is particularly common in southern Europe. In Portugal, Spain and Sicily, according to Caladruccio, 10 per cent of the children are affected. Its distribution is generally more common in warm than in cold climates. It is probably identical with the common rat tape-worm which as been named *H. nana fraterna*.

The adult worm is usually from 10 to 40 mm. long (extremes 5–100 mm.) and 0.5 to 0.9 mm. wide. The parasite is so small and delicate that it resembles a strand of mucus in the faeces and therefore is frequently not found after treatment, even when diligently sought for. It contains from 100 to 200 segments from 0.1 to 0.12 mm. long. It has lateral genital pores, all of which are on the same side. The head (0.3 mm.) has 4 suckers and a retractile rostellum encircled by a single row of 24 to 30 hooklets. The eggs are liberated by disintegration of the terminal segments. They have a very characteristic appearance. They are spherical or oval, about 30 by 45μ in diameter, colorless and translucent. There is a thin outer membrane and an inner membrane leaving a zone about 7μ wide between them. The latter encloses the lemon-shaped embryophore. At each pole of the inner membrane there is a slight protuberance from which arise several long filaments which lie in the zone between the membranes and partly encircle the embryo. The latter contains 6 conspicuous hooklets.

The adults live in the upper ileum and are often numerous, 1000 to 1500 or more. They may then give rise to gastrointestinal and nervous disturbances.

Life History.—Unlike other members of this group, the parasite requires no intermediate host, as was demonstrated by Grassi and Rovelli, (1887, 1892). In rats, and probably in man, the fully embryonated eggs after ingestion pass through the stomach into the intestine, and then liberate the embryos, (onchospheres) which penetrate into the villi and undergo encystment, forming a cysticercoid. After 4 days' development a rostellum with hooklets appears. The larva then leaves the villus, re-enters the lumen of the intestine and attaches itself elsewhere to the mucosa. It develops to maturity in about 15–20 days, so that after about a month eggs appear in the faeces. It is, therefore, easy for the host to become superinfected if faeces are conveyed to the mouth by dirty fingers.

Epidemiology and Prevention.—With this parasite, as it utilizes no intermediate host, infection apparently is transferred commonly from patient to patient. Some observers believe that man is probably the only common source of human infection. However, there has been much dispute as to the identity or otherwise of *H. nana* of man and of *H. nana fraterna* of mice and rats. While human infection has been relatively rare in some northern localities in Europe and Canada where the rodent infection was common, in warmer countries where rodent infections are still commoner, human infections are

frequent also. Grassi has suggested that the human and murine strains are identical. Several investigators have infected children with ova from murine sources and Woodland has infected mice with ova from human sources. Shaw (1932) reported that 2 murine strains were physiologically as different from one another as they were from the human strains.

Chandler in India has found an inverse correlation between the incidence of *H. nana* infection and that of such infections as *Ascaris* and *Trichuris*, which definitely depend on human faecal contamination for transmission. On the other hand, he found a high incidence of *H. nana* infection to be directly correlated with the prevalence of household rodents and conditions favoring their access to food and with such rodent-borne infections as plague and with *Hymenolepis diminuta.* He points out that in the southern United States *H. nana* infections are about equally common in cities with sewage systems and in rural areas and that this is more suggestive of dissemination by rats and mice than by human contamination. The frequency of heavy infections is a further argument in favor of the important role of rodents in transmission, for while the accidental swallowing of a small portion of mouse excrement with food could easily convey one or more whole segments of the worm with hundreds of eggs, such a wholesale contamination from human faeces would be improbable. The question is an important one from the standpoint of prevention. Chandler believes that human infection is commonly acquired from ova derived from rodents and that hence infection can be avoided by preventing access by rodents to human food which is to be eaten without further cooking. However, as it seems probable that infection in man may also be due sometimes to ova derived from another infected human being, sanitary measures in the disposal of excreta are also necessary to prevent spread of infection.

Symptomatology.—The parasite, in severe infections, may give rise to systemic toxaemia with nervous manifestations, especially in children. They may suffer from abdominal pain, diarrhoea, convulsions, epileptic attacks, and insomnia.

The *diagnosis* is usually easily made by finding the ova in the faeces. Like nematode ova, they float in strong salt solution.

Treatment is considered on p. 1472.

Hymenolepis diminuta (Rudolphi, 1819), (Syn. *Taenia diminuta*) the flavo-punctate tape-worm of rats (*R. decumanus*, *Rattus alexandrinus*) has been found in more than 200 human cases. Recently it has been reported more frequently, especially in India, Soviet Russia, the Belgian Congo, Japan, Italy, South America, West Indies, and in the southern United States. Chandler found 23 cases in about 10,000 faecal examinations in India, and no less than 3 in 50 examinations in one locality where the food habits were particularly favorable for infection.

It is much larger than *H. nana*, measuring 20 to 60 cm. long and about 4 mm. wide, containing about 1000 segments. The mature segments are broader than they are long. The head carries small suckers and a rostellum without hooklets. The ova resemble the preceding, but are larger, 50 to 80μ, have a thicker, radially striated, outer membrane, and no filaments. The intermediate hosts are various species of insects and myriapods, including meal and grain insects, and the rat flea. Infection occurs by swallowing an infected intermediate host. The infected insects have been found in dried fruits, breakfast cereals, etc., such insects having become infected from mouse droppings.

Drepanidotaenia lanceolata (Bloch, 1718) (Syn. *H. lanceolata*) common in geese and ducks, has been reported once in man, in Germany. It is from 2 to 12 cm. long and 6 to 12 mm. wide. It has a small globular head with a rostellum bearing 8 hooks and a short neck.

Dipylidium caninum (Linnaeus, 1758), (Syn. *Taenia canina*) the common tape-worm of cats and dogs, and other carnivora has been found occasionally in man, chiefly in

tions, the diarrhoea disappeared a few weeks after the infection became established. The eosinophilia was increased to as high as 38 per cent 5 weeks after the origin of the infection and came down to normal a few weeks later. In the meantime a large number of the parasites present were expelled. The human infections were not transient, the worms being still present and producing ova 7 months after the experimental infection. The infections were severe, as was shown by treatment with tetrachlorethylene. As many as 260 flukes were brought away in the first stool after treatment.

Epidemiology.—Human infection with *Echinostomes* occurs from the fact that the cercariae, after escaping from some small *Planorbid* snail which serves as the first intermediate host, penetrate into and encyst in various other molluscs which are locally eaten. In Luzon, the parasite encysts in the snail *Pila luzonica*, which is eaten raw by the Ilocarnos. The cosmopolitan parasite of dogs and geese, *E. revolutum* is said by Chandler to infect from 3 to 6 per cent of people in parts of Formosa and to result from eating raw limpets. Sandground and Bonne, in their studies in the Celebes, found that practically 100 per cent of the snails were infected in the rice fields in certain localities. About Lindoe, in 3 villages, they found human percentages of infection of 96, 44, and 24. The mussels taken from the lake close to the heavily infected village were found carrying large numbers of *Echinostome* metacercariae. The mussels constitute a prominent article of the daily diet of the local population. They are eaten after passing through a primitive boiling process. Such mussels, on being fed to laboratory bred rats and mice and being eaten by both Bonne and Sandground, produced infections in which the *Echinostomes* were demonstrated. In rats and mice the parasites do not grow as large as they do in man.

In Batavia, Sandground found 22 cases of human echinostomiasis among the lunatics at an asylum for the insane. The normal population living near were not found to be infected. It was found that the consumption by the lunatics of uncooked snails took place, as was directly witnessed by Sandground.

Treatment.—Sandground has treated 11 cases with 2 to 4.5 cc. of tetrachlorethylene (C_2Cl_4). The patients passed from 13 to over 270 worms after the administration of the drug

Prophylaxis.—According to the investigations of Tubangui in the Philippines and of Sandground in Java, the parasite *E. ilocanum* is primarily one of the Norway rat, or field rat. However, the parasite has also been found to be common in dogs in Canton by Chen (1934). Hence all of these animals may serve to disseminate the disease.

Other species of *Echinostomes* recorded from man are: *Paryphostomum sufrartyfex*, a pig parasite, one human case in Assam; *Echinochasmus perjoliatus* and *E. japonicus*, parasites of the cat and dog in Europe and the Far East, which use fish as second intermediate hosts. A few natural and experimental human cases have occurred in Japan. *Himasthla meuhlensi*, one human case thought to have been acquired from eating raw clams in New York. And several other species of *Echinostoma* in Rumania, Russia and Japan, some of which encyst in tadpoles. *E. paraulum*, pathogenic for pigeons, has been reported from man in Russia. A species of *Plagiorchis* has been found by Africa and Garcia at an autopsy of a native of Ilocano, P. I., where the inhabitants eat the grubs of certain insects believed to be the second intermediate hosts of this trematode. Sandground (1940) has reported a second species from a native in Batavia and has named the species *P. javensis*.

Gastrodiscus hominis (Lewis and McConnell, 1876), (Amphistomum hominis), normally a parasite of the pig, has been reported in man in India, China, and the Malay States. The parasite was first found and described by Lewis and McConnell occurring in the caecum in a patient in India, and subsequently redescribed by Leiper and by Stevens. The former created the genus *Gastrodiscoides* for it. It is a relatively common human parasite in Assam. Thus Buckley (1939) found it in over 40 per cent of 221 people examined in 3 villages in Assam, where it was thought to be probably widely

disseminated. The parasite has also been reported from man in Cochin China and from Indian immigrants to British Guiana. It has been suggested that the pig is a common reservoir host in India and Assam, while in the Malay States the Napu mouse deer, *Tragulus napu*, has also been found infected. It has also been found in field rats in Java.

The parasite lives in the caecum and large intestine, where it may give rise to some inflammatory change and may cause diarrhoea. The adult worm usually measures from about 5–7 mm. in length. Some specimens occasionally measure as much as 10 mm. in length by 4–6 mm. in breadth. The adult worms have an orange-red appearance caused by a fine net-work of red capillary-like structures in the cuticle against a flesh-colored background. The body is divided into 2 parts. It consists of a posterior, concave, disk-like portion from which proceeds a teat-like projection bearing an oral sucker. The acetabulum is in the posterior margin of the disk. The ovary is behind the testes. Slightly behind the middle of the anterior portion in the median line is the prominent genital core which characterizes the genus. The ovoidal, operculated ova measure 150 by 72μ. They are rhomboidal in shape, tapering rapidly towards each end. Miracidia develop after the eggs have escaped from their host. However, nothing more of the life history is known. By analogy with other amphistomes there is probably little doubt that the cercariae encyst on various forms of aquatic vegetation and that the life cycle is similar to *Fasciolidae*. The life cycle in the related species, *Gastrodiscus aegypticus*, of the intestine of the wart hog, is believed to utilize the snail, *Cleopatra bulimoides*, as an intermediate host.

Epidemiology.—Although the pig is a common reservoir host in some localities and has been reported by some as a common reservoir of human infection, Buckley found that in some places in Bengal and Assam where the heaviest human infections occur pigs were rare and could hardly have served as a reservoir for human infection. It is presumed that as in the case of *Fasciolidae* man may contract the infection from the ingestion of uncooked forms of infected water vegetation.

Treatment.—Manson-Bahr states that the parasites can easily be expelled from the intestinal tract by thymol and carbon tetrachloride. Chandler, however, points out that the parasite is often not easily removed by anthelmintics but sometimes treatment with high soap water enemas gives good results. Buckley by means of soap water enemas obtained nearly a thousand parasites from an 8 year old boy.

Watsonius watsoni (Conyngham, 1904) (Syn. *Amphistomum watsoni*) is the only other amphistome so far found in man and there has been reported but a single case, from the Nigerian shore of Lake Chad. The patient suffered from a severe, watery diarrhoea which resulted fatally. At autopsy the parasites were recovered from the intestinal wall, some attached to the duodenum and jejunum. Others were free in the lumen of the large bowel. The parasites are reddish yellow in color and thick and pear-shaped, being slightly concave ventrally, with a translucent gelatinous appearance. They measure about 8–10 mm. long by 4–5 mm. wide. The posterior sucker has a diameter of about 4 mm. The oral sucker is sunken and more indistinct. It has a transverse diameter of about 1 mm. It is provided with 2 lateral pouches. The eggs are ovoidal in shape, operculate, and light yellow in color and measure from 120 to 130μ by 75μ. They are immature when laid. The details of the life cycle are unknown. The normal hosts for this parasite appear to be several species of monkeys, in which the parasite has been found in Africa, Malaya and Japan. In French Guinea, *Cercopithecus callitrichus* is recorded as the normal host.

Infection in man is probably contracted as in the case of other amphistomes by ingesting vegetation on which the metacercariae have encysted; hence avoidance of eating uncooked vegetables grown in water which has been contaminated by the ova of the worms would protect against infection.

Paragonimiasis (Endemic Haemoptysis)

The disease is due to infection with the trematode *Paragonimus westermani* (*P. ringeri*), and is characterized by pulmonary symptoms and

by the appearance of rusty brown sputum in which the characteristic eggs of the parasite are present.

GEOGRAPHICAL DISTRIBUTION AND HISTORY

Geographical Distribution.—The disease occurs in the Far East, in New Guinea, the Dutch East Indies, India, and in parts of China, Indo-China, Siam and the Malay States and the Philippines.* Also, especially in Korea, Japan and Formosa, where in some districts from 40 to 50 per cent of the population are infected. In Africa the disease has been encountered especially in the British Cameroons and the Belgian Congo, and in South America, in the Matto Grosso area of Brazil, in Peru, and in Venezuela. The species described as *P. kellicotti* has been found in at least one human case in the United States.

History.—In 1880 Baelz found the ova in the sputum of a Japanese patient with haemoptysis, and in the same year Manson described the disease and found the ova in

FIG. 351.—Sputum of man containing eggs of the lung fluke, greatly enlarged. (After Manson.)

the sputum of a Chinese. Manson's patient subsequently died and at the autopsy a fluke was found in the lungs which was the source of the eggs seen by him in the sputum. However, Ringer (1881) first found the mature parasite in an autopsy in 1879, which was later described by Cobbold under the name of *Distomum ringeri*. Subsequently it was recognized to be closely related to, if not identical with, the previously described *Paragonimus westermani* which Kerbert found in the lungs of two Bengal tigers which died in the Hamburg and Amsterdam zoological gardens. A relatively high incidence of *Paragonimus* infection is found to exist among leopards and tigers in China (Wu, 1939).

Japanese investigators, especially Kobayashi and Yokogawa, have contributed to the elucidation of the complete life cycle.

Etiology.—*Paragonimus westermani* (Kerbert, 1878) and *P. ringeri* (*P. compactus*, Cobbold, 1880) are very closely related or identical flukes which occur as parasites in the lungs of man. They also occur in pigs, dogs, cats, rats, and various wild carnivores, as the tiger, wild cat, panther, fox, wolf and the beaver. The flukes are reddish brown in color and rather flesh-like in appearance, measuring from 8–20 mm. long and 5–9 mm. wide. They are ovoidal in shape, with some flattening of the ventral surface. The oral sucker is terminal or subterminal. A ventral sucker, the acetabulum, is conspicuous and lies just anterior to the middle of the body and close to the common genital

* Miller and Wilbur (1944) have reported 3 cases in Marines from the South Pacific

pore. The testes and ovaries are branched. The ovary and uterus are placed on opposite sides of the body, in front of the testes. The cuticle is covered with scale-like spines. The species are differentiated largely on the arrangement of the spines. In *P. ringeri* they have been described as wedge-shaped and grouped in clusters of 3–12. In *P. westermani*, (the species observed by the writer in the Philippine Islands), they are scattered, and in *P. compactus*, they are said to be arranged in clumps.

A study of the life cycle has demonstrated differences in both the morphology and behavior of the developmental stages between the Korean and American forms, and also between the Korean and Japanese forms. *P. kellicotti*, which has been found in North and South America in the pig, dog and cat and goat, is a rather common parasite of the mink in North America and Canada. At least one case of human infection has been reported in North America. It is believed by some parasitologists to represent a distinct species. However, Chandler (1940) thinks a final settlement of the species of this genus is not yet possible. A selected species has been found in the tiger in the Malay States. Recently Chen has found a form in rats in Canton.

The eggs are dark brown, 90–55μ in size. The shell shows a thickening opposite the operculum which is most marked in *P. ringeri*. They are unsegmented when deposited and require about 4 weeks under favorable conditions for the development of the miracidium outside the body.

Infection of man results from consumption of infected crabs or crayfish, which serve as the second intermediate host in endemic regions. The ova of the parasites, usually coughed up in the sputum and expectorated or swallowed and passed in the faeces, are the source of infection of the intermediate hosts. Hence human infection is often sporadic.

FIG. 352.—*Paragonimus ringeri;* photograph from a sexually immature specimen. (From Tyson.)

The first intermediate host is a snail, of which at least six species of *Melania*, have been found to be effective, particularly *M. libertina* or related forms. In Venezuela where *P. kellicotti* is found, the snail is *Ampullaria luteostoma*. These are operculated aquatic snails attached to stones, etc., in ponds and streams. The cercariae, after escaping from the snail into the water, bore their way into certain species of fresh water crustaceans, the second intermediate host.

The second intermediate host is a crab, a species of the genus *Potamon*, *Eliocheir*, or, in Korea, a species of crayfish, *Astacus*, in which they undergo growth and development for 6 weeks or more. In the United States, Chandler (1940) says *Pomatiopsis lapidaria* serves as the molluscan host of *P. kellicotti*, while probably all the species of *Cambarus* serve as the crustacean hosts (Ameel, 1934). In the human cases of infection of *P. kellicotti* reported in the United States, the patients had eaten crayfish prepared by a German cook. Experimental feeding of puppies with infected crabs has brought about infection with the lung fluke. In Japan and China, these crustaceans are often eaten raw (soaked in spiced wine), but in Korea and Formosa, where the infection is also common, this custom does not prevail, and some believe that the encysted cercariae may enter the body in some other way, perhaps in contaminated water, in which they may live for some time after escape from the second intermediate host.

After liberation from the ingested cyst, the young fluke is believed to penetrate the intestinal wall, migrate through the peritoneal cavity, and burrow through the diaphragm into the lung. Here they mature and are found, often in large numbers, in funnel-like cavities or cysts lined by fibrous walls, which communicate with the bronchi,

giving rise to many of the pathological and clinical features of bronchiectasis. Here they may live for at least 6 years, possibly much longer. The ova are often swallowed in the sputum and may be passed in the faeces. Less often the flukes invade other tissues, including the liver, intestinal wall (when ova also may be found in the faeces), testes, prostate, lymph nodes, skin, muscle, and brain.

Pathology.—On examining the lungs, small brown spots may be thickly distributed over the entire surface of the pleura, and deeper in the lungs many small cysts of a deep red color may occur, in all of which lesions the parasites are found. The flukes are also often found in burrows or tunnels, the walls of which are formed of connective tissue. These lesions or tunnels result from hypertrophy of the bronchioles. Cysts may also be formed from breaking down of the adjacent tunnel walls. Musgrave, in his studies in the Philippines, described (1) non-suppurative areas containing eggs leading to round cell and connective tissue reaction and usually to abscess formation; (2) tubercle-like lesions in which the abscess might contain caseous material; (3) suppurative lesions, and (4) ulcerative, in which the healing was only partial. He also pointed out that the peculiar bluish cyst-like burrows of the parasite occurred in many organs and tissues besides the lungs. Such lesions are encountered, in addition to the lungs and pleura, in the intestine and peritoneum, liver, mesenteric lymph glands, muscles, testes and brain. The intestinal mucosa is a common seat of infiltration and here an inflammatory reaction sometimes occurs, ending in ulceration, with the appearance of the eggs in the faeces. Robertson has reported the presence of ova in the spinal cord which produced during life transverse myelitis.

In the lungs, in advanced cases there may be a picture of generalized or localized acute cirrhosis with cystic dilatation of the bronchi and tubercle-like abscesses. Leucocytic infiltration occurs about the parasites and there is frequently fibrous encapsulation.

Symptomatology.—The case is often considered as one of chronic bronchitis on account of the occurrence of cough and morning expectoration of a gelatinous sputum which is usually brownish or reddish. It is also known as endemic haemoptysis for the reason that after violent exertion, or at times without manifest reason, attacks of haemoptysis of varying degrees of severity come on. The signs on percussion are usually insignificant while those on auscultation at the time of haemoptysis are often marked. The symptoms often disappear for months to again reappear. Bercovitz found that X-ray examination of the lungs was usually disappointing, while lipoidol infiltration revealed no cavities, probably because the *Paragonimus* infection occurred particularly at the periphery of the lungs. However, Wang and Hsieh (1937) found there were shadows of infiltration which are direct evidence of *Paragonimus* infection and therefore of definite diagnostic value. In some instances the physical signs may suggest broncho-pneumonia or pleural effusion.

The course of the disease is very chronic, often lasting many years As a rule, the patient is fairly well nourished, although recurring attacks of haemoptysis may bring on a rather marked anaemia. In the intestinal

of brood capsules and of scolices in each capsule. Growth may continue for several years (2 to 8), and the cyst may become as large as a child's head (although usually they are much smaller). It has been estimated that as many as 2,000,000 scolices may thus arise from a single ovum. Occasionally a cyst is barren, contains no scolices. When the contents of a cyst are eaten by a dog, each scolex may develop into an adult worm.

In some cases in which no effective encapsulation occurs the daughter cysts develop as a result of evaginations of the cyst wall. This results in the formation of a mass of small discrete vesicles, like a bunch of minute grapes, which tend to infiltrate the surrounding tissues and even to metastasize to other organs like a malignant tumor ("Gallertkrebsen"). They occur most often in the liver, especially in cattle. Because these *multilocular* or *alveolar hydatids* are common in man in certain districts (southern

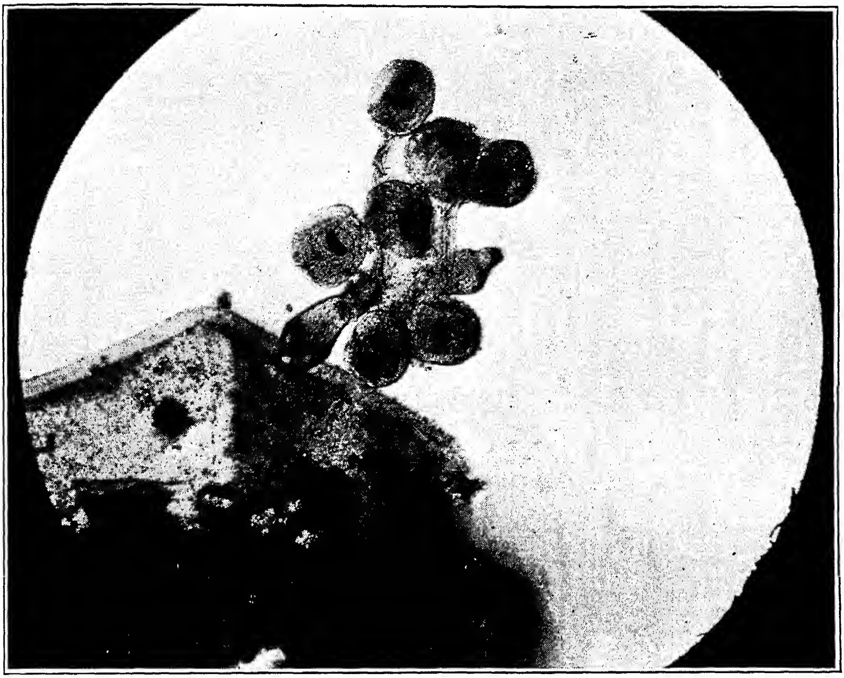


FIG. 358.—Echinococcus cyst wall with a ruptured brood capsule showing scolices. (From U. S. Naval Medical Bulletin.)

Germany, Russia) but are almost unknown in others (Iceland, Australia), some have regarded the parasite as a distinct species, *E. multilocularis;* the present evidence is against the idea that this is a distinct species.

Clinical Symptoms.—The cysts eventually cause grave injury as a result of pressure and destruction of the organs involved. In the liver the early stages are usually symptomless, or a tumor may be felt. Large cysts on the convex surface may be mistaken for a pleural effusion. If the contents become infected the symptoms are those of abscess. Rupture may occur spontaneously, either into the peritoneal cavity, pleura or lung, less often into the gastrointestinal tract or into the tissues, and usually causes a violent reaction which may be fatal. Anaemia, emaciation and weakness develop, and death usually occurs within a few years unless complete surgical removal is possible.

Involvement of the lung may occur in as much as 12 per cent of the cases in some series, and is even more serious. The cysts are most often in the right lower lobe. The early symptoms are cough, slight haemoptyses, and transient fever. Localized

râles, may suggest early tuberculosis. Later the symptoms and signs may be those of tumor or abscess. Rupture may occur into a bronchus, the pleural cavity, or both. If such an accident is not quickly fatal, recovery may occur spontaneously or after suitable surgical drainage. The sharp outline of the cyst in roentgenograms is characteristic. Eosinophilia is often present. Hooklets may usually be found in the sputum, after rupture into a bronchus, if search is prolonged.

Diagnosis.—Clinical diagnosis is often difficult. Since the liver and lungs are especially involved and the other organs much more rarely infected, differential diagnosis is usually a problem of the consideration of abdominal and pulmonary disorders.

The symptomatology is in no way characteristic and the disease may at times simulate hepatic cirrhosis, cholecystitis, abscesses of the liver and lungs, early tuberculosis, and various new growths arising in the chest or abdomen. Degenerative cysts not infrequently undergo calcification, in which case they may frequently be detected by X-ray examination and present a typical appearance. Rupture of the cysts occurs not infrequently and may be followed by severe or even fatal anaphylactic reactions. Ruptured cyst of the liver, as well as of the lungs, may discharge through the bronchi and diagnosis can be made by the finding of characteristic hooklets in the sputum. An eosinophilia is found in only about 20–25 per cent of echinococcus infections.

However, a definite diagnosis may be made:

1. By examination of fluid from a cyst obtained at operation (or autopsy). Exploratory aspiration is dangerous. If leakage of fluid occurs, or if a cyst ruptures, a violent reaction, anaphylactoid in type, may follow and an eosinophilia (confined to the region of the cyst) may occur. If scolices are scattered, they tend to become implanted and give rise to new cysts. The cyst fluid is clear and according to some analyses contains about 0.5 per cent of NaCl, a trace of sugar, and no albumin. According to Lemaire and Ribere (1935) it may have a specific gravity of 1.01 plus, a *p*H of 6.7, and contain ammoniacal salts, creatinin, inosite, lecithin, and both proteolytic and glycolytic enzymes. The clinical symptoms which have formed the basis for supposing a "toxin" to be present in the cyst fluid are perhaps rather manifestations of an anaphylactic reaction. Diagnosis of material from a cyst depends upon finding free scolices or scattered hooklets from disintegrated scolices. These are 25 to 40μ long, and have a characteristic shape. The appearance of a fragment of the curled laminated cyst wall is also decisive.

2. By the *precipitin test* of Welch and Chapman. Equal parts of patient's serum and clear hydatid cyst fluid are mixed and incubated one hour at 37°C. A positive reaction (a precipitate) is obtained frequently if the antigen is good, but false positive reactions occur.

3. By the *complement fixation test* of Weinberg and Parvu. The usual Wasserman technique is followed, using as antigen 0.4 cc. (or 1/3 to 1/4 the anticomplementary dose) of cyst fluid. The fluid may be obtained from sheep cysts, and is filtered, carbolized and inactivated before use. The results appear to be reliable, but there is difficulty in preserving the antigen. Fairley and Kellaway (1933) who have had extensive experience in Australia with both these tests and the Casoni test, to be described presently, obtained positive reactions in about 85 per cent of the cases. However, they thought the Casoni cutaneous test is somewhat more sensitive than the complement fixation one.

4. By *cutaneous allergic tests* (First described by Casoni, 1912). About 0.2 cc. of hydatid cyst fluid is injected intradermally or applied to a scratch. A positive reaction, consisting in the rapid appearance (usually in 20 minutes) of a large wheal with a zone of erythema, has been reported in about 90 per cent of the cases. There may be a marked secondary late reaction also. Sensitiveness may last long after removal of the cyst.

Dennis (1937) has prepared a more stable hydatid antigen from cysts of infected cattle and sheep by centrifugation and evaporation. Dry precipitate was obtained and diluted 1:10,000 in physiological salt solution and 0.2 cc. of the antigen employed for an intradermal dose.

Rose and Culbertson (1940) have pointed out that neither cutaneous testing nor complement fixation have been employed in many countries, as in the United States, on account of the scarcity of hydatid fluid. Also, the different samples may show wide variations in antigenic potency, and the specimens deteriorate more or less rapidly. The observations of several investigators have suggested that the Casoni and the complement fixation tests are not species specific but actually group specific, and the reaction has been obtained with antigens prepared from other cestodes than hydatid (Morenas, 1932, Outeirino, 1935, and Chung and Tung, 1939). Chung found the reaction also positive in 4 of 9 cases of kala-azar.

Rose and Culbertson have prepared antigens from (1) *Cysticercus pisiformis*, a larval stage of the dog tape-worm, *Taenia pisiformis*—(Syn. *T. serrata*) which occurs naturally in the liver of rabbits and in from 50–60 per cent of stock laboratory rabbits, and (2) from *Taenia taeniaeformis*, the adult tape-worm found in the intestine of cats and very common in this animal, hence antigens from both are easily obtainable.

The antigen from *Taenia pisiformis* is prepared by dissecting out the larvae from the cysts. They are then triturated under sterile conditions in physiologic salt solution containing 0.5 per cent phenol. The supernatent fluid is used after centrifugation and final sterilization. In the case of *Taenia taeniaeformis*, the antigen is made from the adult parasite found in the intestine of the cat, prepared in a somewhat similar manner.

They have performed cutaneous tests in 14 patients suffering from Echinococcus disease. Positive cutaneous reactions were obtained in 12 out of the 14 cases. They also obtained a complement fixation test with serums of 7 patients with known hydatid disease with these substitute antigens.

Treatment.—All treatment other than surgical has proved to be unsuccessful. Surgical procedures are of benefit only in the case of unilocular cysts in sites which are operable. If removal is attempted, the cyst should be excised intact, or else the wall should be stitched to the abdominal wall and allowed to heal by granulation (marsupialization). It is advisable to inject some antiseptic fluid into the cyst to kill the scolices before undertaking any manipulations which might result in accidentally scattering the contents of the cyst.

The dangers of withdrawing fluid directly have already been referred to and it has been suggested that it is desirable after aspiration of a portion of the contents to immediately inject 10–15 cc. of a 10 per cent formalin solution to kill the scolices, brood capsules, etc., and then withdraw the fluid in 5 minutes, before proceding to the removal of the cysts. Some surgeons prefer to close the cavity without open drainage, as the procedure known as "marsupialization" requires longer hospitalization.

Prevention.—Since human infection may result from fondling infected dogs or perhaps from ingesting ova of the parasite from the ground on which dogs have defecated, or on vegetation contaminated with their faeces, thorough washing of the hands before eating is advisable. Dogs should be prevented from eating the carcasses of sheep, cattle and hogs in the endemic areas. The disease has been greatly reduced in Iceland in recent years as the result of a campaign enforcing the burning or burial of infected material and of the law controlling dogs by taxation and treatment. Lack of personal hygiene among sheep breeders in Argentina has apparently been responsible for a considerable increase in human infection in recent years. According to Greenway, the disease quadrupled in that country between 1901 and 1921.

Fish Tape-worm Infection

Diphyllobothrium latum (Linnaeus, 1758) (Syn. *Dibothriocephalus latus*), the broad Russian tape-worm or fish tape-worm, is common in Scandinavia, the Baltic countries, Russia, Northern Italy, Switzerland,

Bavaria, Rumania, Palestine, Siberia, Central Asia, Japan, Central Africa, especially among the natives around Lake Ngami.

In some localities in Europe, 80–100 per cent of the people are infected. In East Prussia, Chandler asserts nearly all the fisher-folk become infected by eating "raw burbot" liver spread on bread. In recent times, Baltic immigrants, who came into the United States in connection with lumbering operations, have been responsible for the establishment of endemic centers in northern Minnesota and Michigan, southeastern Manitoba and the lake districts of Ontario. Except possibly for Africa, the infection is not indigenous outside the cooler zones of the northern hemisphere. Man is an important host and the parasite is also harbored by dogs, cats and bears, which become infected by eating raw fish.

Morphology.—The head is olive-shaped, 2.5 mm. in diameter and has 2 deep suctorial grooves (bothria) on each side but neither rostellum nor hooklets. The body attains a length of 30 feet (rarely even 60 feet) and may contain 3,000 or 4,000 segments which are about 12 mm., rarely 20 mm., broad and 5 mm. long. If several worms are present, they are smaller. The uterus is rosette-shaped, and there is a ventrally placed genital pore. Each mature segment is continuously discharging eggs which are present in large numbers in the faeces (estimated at 36,000 per day). They are operculated, brownish in color, 45 by 70μ, with a thin shell enclosing a central mass of granular spherical segments.

Life History.—When the eggs reach fresh water, if the temperature is favorable, segmentation proceeds, and after three weeks the operculum opens and a ciliated embryo, the coracidium (six-hooked onchosphere), 25 to 30μ, escapes. It can live several days in water, swimming about until it is swallowed by a cyclops (*C. strenuus*, *Diaptomus gracilis*, *D. oregonensis* etc.), the *first intermediate host.* It loses its ciliated covering, pierces the gut wall, and after 15 days' development in the tissues becomes a *procercoid larva*, an ovoid structure 50μ long with a spherical protuberance at one end containing six hooklets. When the cyclops is eaten by certain fresh water fish (pike, pickerel, perch, trout, salmon etc.), the *second intermediate host*, the larva penetrates the stomach wall and passes into the muscles or other tissues. Here it develops into a *plerocercoid larva* or *sparganum*, a worm-like organism 8 to 16 mm. long with suctorial grooves at its anterior extremity. When the raw fish is eaten by man or other suitable definitive host, the larva is liberated in the small intestine and develops rapidly into the adult form. After 18 days it may reach a length of two feet and begin to discharge eggs. It may live for years, even it is said for 16 years.

Pathological Effects.—In many cases the symptoms are not noteworthy. The common effects of infection are abdominal pain, loss of weight, and progressive weakness, and other disturbances referred to under infections with *Taenia saginata* (see p. 1464). Tarassov (1937) after experimental self infection, suffered from marked abdominal pain, lost 17½ lbs. in weight, and became so weak that it was necessary for him to enter a hospital.

This parasite, however, is unique among the other human tape-worms in that for many years it has been associated with a very severe anaemia of the pernicious type in which the corpuscles may be reduced to one million per cubic millimeter or less. Such an anaemia, however, only occurs in a very small percentage of the cases. Thus in Finland, where the inhabitants are said to be more prone to *Diphyllobothrium* anaemia than other races, the anaemia rate is only 1 or 2 per 10,000 infections. There is considerable evidence that the role of the worm in the production of anaemia may constitute a trigger mechanism precipitating the anaemia in individuals who have a hereditary or racial tendency to it, but who

may not suffer from the anaemia in the absence of the *Diphyllobothrium* infection. The fact that alcoholic extracts of the parasite may precipitate pernicious anaemia in individuals who have previously had tapeworm anaemia suggests that some constituent of the worm may inhibit or destroy the early pernicious anaemia factor produced by the stomach. However, in some instances the tape worm anaemia has responded to liver therapy, even without removal of the worm as is sometimes seen in ancylostomiasis.

Taenia Anaemia (Diphyllobothrium).—There has been much discussion about the role that this parasite plays in the production of severe anaemia. Schauman, who studied the question for many years (1894–1925 in Finland), maintained that the parasite causes an anaemia not distinguishable from pernicious anaemia, and that the reason that anaemia was not more frequent in cases of infestation was because the majority of individuals were refractory toward the agent of the tapeworm which causes anaemia.

The work of Birkeland, who collected the literature and wrote a monograph on the subject in 1930 (published 1932) is much quoted in the textbooks in recent years. A study of his monograph shows that more than 35 cases of infections in Americans and Canadians, or 14 per cent, showed anaemia.

Slydenhelm thought he could demonstrate in the groundup body of the fish tapeworm a substance which had a haemolytic action both in vitro and in vivo.

In recent work upon the subject, Plotz in New York observed one severe case of anaemia in 25 cases of infestation. Cushing and Bacal in Montreal had 6 severe cases of anaemia among 40 of the tape-worm. Magath, at the Mayo Clinic, found no coincidence of pernicious anaemia with *Diphyllobothrium* infection. However, there had been only 12 cases of *Diphyllobothrium* infection at the Clinic.

Wardle, Gotschall and Horder (1937) have made a careful study of the infection in dogs. A series of normal dogs were first carefully studied and then fed plerocercoids in fish muscle. The dogs were allowed to remain infected from 4 to 13 weeks. A decline in the red blood corpuscles was not evident until about the sixth week of infection. By the thirteenth week, the red blood corpuscles had fallen to an average of 3,390,000. The haemoglobin fell in proportion.

Mueller (1938), in a study of infection with *Diphyllobothrium mansonoides* in cats, gives evidence of severe anaemia developing in the animals as a result of the infection.

Totterman (1939) gave to 9 patients with a history of anaemia from *Diphyllobothrium* infection daily by mouth for 2 to 4 weeks 0.3 gram of dried worm, or the corresponding dose of an alcoholic extract. In 5 of them the number of red cells fell sharply to as little as a million, but the haemoglobin did not fall, or did so but slightly. Accordingly, there was a rise of the color index, but immediately on ceasing the administration of tape worm substance the blood condition began to improve, returning to normal in a few weeks.

When one of those reacting positively became infected with the tape worm there followed a deterioration similar to that observed in the experiments. There was no great alteration in white cells. The residue of the power after extraction with alcohol had no effect on the blood. Of the other 4 patients, 2 reacted to the worm extract

slightly and 2 not at all. There was no reaction to the worm preparation in 3 persons with a normal blood picture and in 3 with cryptogenetic pernicious anaemia. Perhaps the sharp fall in the number of red cells indicated a mechanism of hypersensitivity. In cases of infection in which the anaemia was of the pernicious type, it improved rapidly on deworming. As to whether the infection causes anaemia, the number of cases were too few from which to draw safe conclusions.

Sievers, using the complement fixation reaction, has found that antibodies are provoked in the serum of patients who had previously suffered from tape worm anaemia on the administration per os of either alcoholic extract of *D. latum* or of dried powdered worm. Controls, however, were negative. Worm antibodies obviously ensued in the human organism on immunization per os, and patients who had suffered previously from *Bothriocephalus* anaemia reacted more readily.

Treatment.—For the treatment of the worm, most authors have regarded oleoresin of *Aspidium* (male fern) (*Dryopteris filix mas*) as the most satisfactory drug, (contraindicated in nephritis and pregnancy). (See p. 1472 for details of treatment.)

Sandground (1938) has called attention to the fact that there has been an appreciable number of fatalities following the administration of male fern, and that the use of the drug certainly calls for caution. In the study of 38 cases of tape worm infection, 5 of which were due to *Diphyllobothrium latum*, he found that carbon tetrachloride was very efficient for treatment. In 12 of 16 cases treated with this drug, the usual dose being 4 cc., the parasite was effectively eliminated. In 3, the results could not be followed up, and in 1, the patient was unable to retain the drug. He thinks carbon tetrachloride is the most effective remedy for the treatment of tape-worm infestations in man. However this drug also sometimes causes death and must be employed with caution. The dose for adults should not be over 2–3 cc. It is especially contraindicated in cases with ulceration of the small bowel, nephritis, pregnancy, and cases where there is fever and evidence of serum calcium deficiency. Sandground (1941) has reported 2 cases with coma following its use.

In all cases of Diphyllobothrium infection in which there is anaemia, treatment should be given as for pernicious anaemia. The anemia usually responds readily to liver therapy.

Prevention and Control.—Prevention depends on the careful abstinence from fish which has not been thoroughly cooked. The public should be instructed regarding the dangers from eating half-cooked fish and cooks should be warned not to taste raw or half cooked fish in connection with flavoring. Bergeer advises that in the endemic regions persons should be warned to cook fish twice as long as they are accustomed to. Children should not be allowed in kitchens and in fish markets. Feeding raw fish to dogs and cats should be discouraged.

Diphyllobothrium mansoni (Cobbold, 1882) (*D. erinacei*, Iwaka, 1933), is an allied but much smaller species found in the dog, cat, wolf, fox, leopard and tiger, and related carnivores in Japan, China, British Guiana, Australia and East Africa. The parasite seldom attains a length of more than 60 or at most 100 cm. The ova are narrower and more ellipsoid than those of *D. latum*. The normal intermediate hosts are (1) a cyclops, and (2) either a frog or a snake. A number of human infections with the plerocercoid stage have been reported.

SPARGANOSIS

Sparganum mansoni (Cobbold, 1882).—The plerocercoid larval form of *D. mansoni* known as *Sparganum mansoni* has been recognized as a parasite of man for many years. It was first named by Cobbold and first described by Manson (1882) who found it in performing a post mortem examination on a Chinese in Amoy. Manson-Bahr, 1940, states that since that time at least 60 human cases have been reported. Yamada and Yoshida elucidated the life history, the whole cycle being worked out by Okumua in 1919. It was shown that the larval forms could develop into Diphylobothriids, and the term "Sparganum" is a group name for such plerocercoids. The *Spargana* which develop in man and other land animals, (amphibians, reptiles, rodents, etc.) all belong to the *Spirometra* subgenus or group, characterized by having separate openings for cirrus, vagina and uterus, while in *D. latum* there is a common opening for the cirrus, and vagina. Unlike *D. latum*, they infect cyclops instead of *Diaptomus* as intermediate hosts.

Sparganum mansoni in form resembles ribbon-like strings of fat 3–12 inches long and may be encapsulated in many different tissues, not rarely in the conjunctiva where they may cause serious disturbances. The largest number of cases have been reported from Indo-China, China and Japan, and perhaps this species has been encountered in the United States. Also, scattered cases of closely related larvae are known from almost every part of the world.

Human infection might come from swallowing infected cyclops in contaminated drinking water. There is evidence, however, that infection may be brought about by the Chinese custom of applying split live frogs as a dressing or poultice to sores on the hands, or in the vagina, or in the eyes, the parasite migrating from the frog into the tissues of the wound. Such *Sparganum* infections give rise to a large amount of eye diseases in some localities, which may be serious. Under normal conditions the plerocercoid stage is passed in the frog, *Rama nigromaculata*, or a snake, *Elaphe climacochora*, and the procercoid in the cyclops, *C. leuckarti*.

There is much confusion about the differentiation of the species of the *Spirometra* group of *Diphylobothrium*, all of which are primarily, when mature, parasites of carnivora. Faust, Campbell and Kellogg (1929) described 6 species in China, but more recently Iwata (1933) concluded that all the members of the group belong to a single species, *D. erinacei*, since he could find in the proglottides of a single worm all of the types of structure described for the different species. However, there are biological differences in some. Thus the Chinese *S. mansoni* develops more rapidly in mice than in frogs, and the American *mansonoides* fails to develop in frogs at all, but develops readily in mice.

The form described as *Sparganum proliferum* (Ijima, 1905, Stiles, 1908) is a plerocercoid larval form of a tape-worm of which the adult form is unknown. It has been reported in 6 human cases in Japan and in a fisherman in Florida. In the Japanese case, Tashiro found thousands of the larvae in the subcutaneous tissues, intermuscular fasciae, the mesentery, walls of the intestines, kidneys, lungs, heart and brain. On ingestion of these larvae by vertebrates, they are digested and destroyed, but transplantation into the subcutaneous tissues or peritoneal cavity of mammals permits them to live and multiply in the tissues asexually by forming lateral buds. Mueller (1938) from a careful restudy of specimens of *S. proliferum*, concludes that they are abnormal, degenerate forms without scolices occurring in an unfavorable host (man) and so far they have only been found in man.

A number of other cases of *Sparganum* infection have been reported in the United States, but Chandler (1940) points out there is no information as to the species to which

they belong. However, *D. mansonoides* has a wide distribution in cats in the eastern United States and uses wild species of mice for development of the *Sparganum*. Mueller and Goldstein have shown that when the young *Sparganum* of this species are experimentally implanted in human flesh they grow normally. A few cases have been reported in which the *Sparganum* apparently multiplies in the body by end-like growths. Thousands of worms, usually only 3–12 mm. in length, but sometimes larger, may be present in acne-like nodules in the skin.

Pathogenicity and Symptoms of Sparganosis.—The invaded cutaneous tissues, when they become distended by the developing larvae, frequently become oedematous and painful to the touch. When opened, the larvae may frequently be found contracting and elongating, but in other instances they are degenerated and sometimes enclosed in caseous masses. More or less local inflammatory reaction is encountered.

Ocular sparganosis, especially described by Casaux and more recently by others, has been encountered, especially in French Indo China and about the Tonquin delta.

Joyeux (1939) has observed 14 cases of sparganum infection of the eye in Tonkin, all following poultices of the tree frog, *Rana Limnocharis*. Either the emptied abdominal cavity or a part of the thigh, or even the whole animal, is used to make the poultice. He thinks this method of treatment is employed because the frog is cold blooded and hence believed able to quench fiery inflammation. He has observed that the parasite may settle in the lids or it may penetrate the orbital fat or burrow towards the surface, the face, the temple, the root of the nose, or the region of the cheek. The globe of the eye is not penetrated, though secondary bacterial infection may cause it.

The presence of the larva of the non-proliferating type in the eye is usually characterized by pain, redness and oedema of the eyelids, with lacrymation and sometimes marked ptosis. The larvae have been found under the conjunctiva, and nodules frequently form around the parasite in the conjunctival tissues. Invasion of the retrobulbar region may give rise to lagophthalmos and ulceration of the cornea. In the cases in which the lesions are confined to the skin, due to the proliferating larvae acne-like pustules may develop and the surrounding tissue may become honeycombed by the parasites, which when they invade the lymph channels may produce oedema and elephantiasis.

Mueller (1938) has studied the infection experimentally in animals. He found that when the parasite is swallowed by various hosts it penetrates the wall of the intestine, reaches muscle, and continues to grow. It travels for some distance laterally under the peritoneum before piercing it, and therefore the intestinal contents do not escape into the peritoneal cavity. The adult parasite taken from the cat and transplanted into tissues of the mouse lives and grows for about 3 weeks. The rhesus monkey will harbor plerocercoids to the number of 600 and will develop a condition of gelatinous swelling in the lower part of the trunk, due to burrowing and disintegration of *Spargana* in subcutaneous tissue. If, however, the monkeys have received previously injections of tapeworm substance this swelling does not occur, since the parasites are promptly encapsulated. In various hosts, the infection leads to an eosinophilia.

Treatment.—Heller reports that he has treated successfully 12 cases with ocular lesions by intravenous injections of novarsenobenzol, 30 cgms. per dose for adults, 7–15 cgms. for children, over 4 or 5 days for 2–6 administrations. Tarsorrhaphy was undertaken to preserve the cornea until the worms had been killed and absorbed or discharged. Cornet (1939) advocates surgical measures in the ocular form in preference to the use of novarsenobenzol. In accessible sites, surgical treatment is rapid. For

retrobulbar infection, however, he found it was sometimes necessary to inject 2–4 cc. of 40 per cent ethyl alcohol with novocaine into the lesions to kill the parasite. In other instances, attempts were made to attract the parasite to superficial sites by applied heat.

Prophylaxis.—For the prevention of the infection in endemic areas, all drinking water which may possibly contain cyclops should be boiled or carefully filtered. The public should be educated with reference to the danger of applying split, fresh frogs as poultices to inflamed or ulcerated areas of the skin or conjunctiva, or other mucous membranes.

Rare Tapeworm Infections in Man

Bertiella studeri (Blanchard, 1891).—This parasite was first obtained from an orangoutang in Borneo and has since been found in other primates in Asia, Africa, and Cuba. In the Philippines, the dog has been found infected. A number of human cases have been reported in these localities.

A related species, *B. mucronata* (Meyer, 1895), has been reported as an intestinal parasite of a man living in Cuba who was an immigrant from the Canary Islands. It has also been recorded from the African chimpanzee.

Kouri (1940) reported 6 cases of tape worm infection among children in Cuba. The parasite was referred to the genus *Raillietina* and named *R. cubensis.* Subsequently a total of 18 cases were found, which seems to substantiate the opinion that the incidence of this species in Cuba is much greater than was hitherto suspected. After further study the parasite has been named *Inermicapsifer cubensis.* Kouri found that the parasites could be expelled easily by anthelmintic treatment, but one instance of a boy who passed proglottides for a period of 6 years suggests that it is not a transitory or temporary parasite.

In addition to this parasite, Cram (1928) and Cameron (1929) found a second species of this family Anoplocephalidae, probably *Bertiella studeri,* in this same district in Cuba, and Roy (1938) has reported another case in a boy aged 8 in India.

Stunkard (1940) has shown that oribatid mites may serve as intermediate hosts of *Bertiella* and other anoplocephaline tape worms

Africa and Garcia (1935) believe that in the Philippines *Bertiella* is acquired from monkeys, and Kouri thinks that *I. cubensis* is a natural parasite of some lower animal, possibly the rat. Other species of this genus occur in rodents in Africa.

The presence of parasites of the genus *Bertiella* in the intestine apparently causes no unfavorable symptoms.

Multiceps multiceps (Leslie, 1780) (Coenurus cerebralis).—This parasite develops as a Coenurus in the brain of ruminants and causes "gid" in sheep. Five authenticated cases of *Coenurus* infection in man have been recorded. One case of *Multiceps multiceps* occurred in the brain, causing epilepsy. The other 4 were found in connective tissue or muscle. One of these was reported as due to *M. glomeratus* (*Multiceps glomerulatus,* Raillet and Henry, 1915), which had previously been found in a gerbille, and 2, and probably all 3, of the others were due to infection with *M. serialis* (Gervais, 1845). *M. serialis* is parasitic as an adult in the intestinal tract of the dog, wolf and fox. As a *Coenurus,* it develops in the intramuscular connective tissue of various rodents. In the human infections with this species, the parasite was found in subcutaneous nodules or tumors (Brumpt, 1934). All the species of *Multiceps* resemble *T. saginata* in their anatomy except in minor details, and have crowns of large hooks similar to those of *T. saginata.* Cannon, (1942) reports a 6th case, the parasites being in intramuscular connective tissue, while Clappum (Journal Helminthology, 1941) reports the second instance in which *Coenurus cerebralis* was found in the brain.

Taenia taeniaeformis (Batsch, 1786), is a normal parasite of the intestine of the cat. The cat becomes infected from eating rats harboring the *Cystercercus* stage. A single human case has been reported in a child in Buenos Aires. The infection is regarded as accidental and probably resulted from eating an infected rat.

Diplogonoporus grandis (R. Blanchard, 1894), a tape-worm with 2 complete sets of genital organs in each segment is from 1.5 to 6 meters long, and the mature segments are about 2.5 mm. broad, and 0.5 mm. long. The ova are operculated, about 50 by 65μ. The life history is not known. Infection is probably acquired by eating raw fish, which are believed to be the second intermediate host. Normally it is a parasite of whales. It has been reported in 6 cases of intestinal infection from Japan. The symptoms described have been colicky pains in the abdomen, alternating diarrhoea and constipation, progressive secondary anaemia, increased pulse rate, and lassitude. The parasites may be expelled by administration of oleoresin of aspidium, or carbon tetrachloride.

Digramma Brauni (Leon, 1907).—Two Rumanian patients have been reported as parasitized by this parasite. Baer regards it as an immature avian species accidentally acquired from eating raw fish.

Ligula intestinalis (Goeze, 1783) has been reported in a Rumanian and a French patient. It is a natural parasite of piscivorous birds. In the first case, it was found in the vomitus of the patient. The parasite in the second case was regarded as immature.

Mesocestoides, Chandler (1942) has reported the first case of human infection with the species of this genus. It conforms closely in most respects with a species recently found by him in raccoons, *M. variabilis*. The child which harbored the worms, was fretful and anaemic; had poor appetite and complained of abdominal pain.

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Chapter L

ARTHROPODS IN THE TRANSMISSION AND PRODUCTION OF DISEASE

The class Arachnida and the class Insecta belong to the phylum Arthropoda. This phylum contains a greater number of species than does any other phylum; in fact it exceeds in this respect all other phyla combined.

Other arthropods are the Myriapoda, or thousand-legged worms, and the Crustacea, to which belong the lobsters, crabs and water-fleas—important zoologically but of very slight importance medically. For Venomous Arthropods, see page 1538.

The different classes of Arthropoda resemble the segmented worms but have as the point of distinction the possession of jointed appendages which proceed from the somites in pairs. Some of the pairs of limbs are for locomotion; at times, certain ones may be specialized for food taking.

The somites or divisions of the body have a chitinous exoskeleton. Respiration takes place through the medium of gills in the Crustacea and by tracheal tubes in the Myriapoda, Arachnida, and Insecta.

The Arachnida have no antennae whereas the Myriapoda and Insecta have a single pair of antennae, the former having numerous pairs of legs or jointed appendages whereas the latter have only three pairs of legs. The Arthropoda have an exoskeleton which is more or less unyielding from the deposit of chitin in the cuticle. This cuticle is not true skin but only a secretion of the epidermis.

Within this external skeleton there is a dorsal digestive system and a ventral nervous system.

Great Importance of Arthropods in Medicine.—Members of this phylum are important not only because of certain immediate and direct effects of their activities, such as the action of poisons introduced by scorpions, spiders and ticks, or the painful and peace-disturbing attacks of various biting arachnids and insects, but in vastly greater degree in that among them are our most important transmitting agents of disease. The following is a list of the diseases transmitted by them.

Transmitted by Arachnids.—Rocky Mountain spotted fever, tsutsugamushi and other typhus-like diseases, tick-bite fever and the relapsing fevers of East and West Africa and of Panama.

Transmitted by Insects.—Typhus fever, European and Indian relapsing fevers, trench fever, American and African trypanosomiasis, plague, tularaemia, filariasis and loaiasis, malaria, yellow fever, pappataci fever, dengue, oriental sore and probably other forms of leishmaniasis, together with certain helminthic infections (*Dipylidium* and *Acanthocephala*).

It is rare to find males. Stokes (1936) stresses the occurrence of various allergic manifestations from sensitization to the protein of the itch mite. Infection results from the passage of male and female mites or of an impregnated female from an infected to a healthy individual. Usually this occurs by contact and commonly at night. As, however, Gerlach has demonstrated, the mites may live in dry, warm air for 3 or 4 days, it is evident that infection may occur from bedding, towels, or other articles that come into contact with the infected skin. Chandler (1940) reports he once witnessed an epidemic of scabies arising from the use of an infected wrestling mat in a gymnasium. Scabies may cause considerable disturbance among troops. Sometimes a single infected individual in a camp where the inmates are closely confined may cause infection of the entire group.

For treatment, it is advisable that there should be a thorough scrubbing with green soap and warm water for 15 minutes. Then the patient should take a warm bath, remaining in it for 30 minutes at least. This softens the skin, especially of the mite burrows. Then there should be rubbed in thoroughly, advisably with a toothbrush and persistently for 20 minutes, an ointment of 5 per cent sulphur in lard. The burrows should be especially scrubbed with the toothbrush and the acari removed or destroyed. The patient should go to bed thus anointed. The next morning he should take a bath and put on fresh clothing, or clothing that has been boiled to kill the eggs or scabies mites. This first course of treatment does not kill the eggs, though it usually kills the adults and immature mites, so about 10 days later a second treatment with ointment as before must be carried out. In cases, as in the field, where it is sometimes impossible to secure the most appropriate treatment outlined, application of sulphur ointment or of Ung. Hydrag. ammoniat, 1 dram to the ounce, is frequently effective if *rubbed in thoroughly* on several successive days. Many skins will develop a sulphur itch if the treatment is applied for too long. Bed clothing and personal clothing must be boiled or baked. A tumbler in the laundry will destroy the mites in blankets and woolen clothing, as steaming or boiling blankets usually ruins them.

Manson Bahr states that a Danish preparation, kathiolan, a special ointment containing potassium sulphide, is used in the British Army.

Prevention rests upon avoiding contact with infected individuals and avoiding the use of infected towels or getting into contact with infected bed linen.

Craw-craw.—This is a rather chronic papular skin disease which is not uncommon on the west coast of Africa. These papules may be as large as a small pea and are quite as hard. They are found chiefly on the legs and arms. The proximal lymphatic glands may be enlarged.

Undoubtedly many of the cases called craw-craw are due to the itch mite. In fact, on the African expedition of 1930 *Sarcoptes scabiei* was demonstrated by Bequaert and Theiler in a number of cases in the scrapings from the skin. Blacklock concluded that in many parts of West Africa craw-craw was usually due to this mite. However, the name "craw-craw" has also obviously been applied to other skin infections in which somewhat similar lesions are present. In some instances in which papulo-pustular dermatitis is present, the lesions have been shown to be due to miliary abscesses in the epidermis produced by bacteria.

Loewenthal (1939) points out that the condition may have a varied etiology and that in some instances it may be really a form of cutaneous onchocerciasis. Formerly O'Neil reported the presence of a larval filaria in the lesions and Mackfie also reported a species of filaria somewhat resembling *Acanthocheilonema perstans*.

In cases due to the itch mite, treatment should be similar to that already described under scabies. In the papulo-pustular form, there should be disinfection of the surfaces with a strong antiseptic, followed by compresses of saturated solutions of boric acid, followed by boric acid or salicilic acid ointments in a strength of 5 per cent.

Different animals have different species of itch mites. The term "mange" is usually applied to infestations of domesticated animals. A serious mange of cats (*Notoedres cati*) may attack man, but the infestation in man quickly dies out (10 days).

Demodicidae (Hair Follicle Mites)

Demodex Folliculorum.—This is a vermiform acarine about 400μ long, living head down, chiefly in the sebaceous glands of nose and forehead. The eggs are about 75 × 35μ. A six-legged larva hatches from the egg and develops into an eight-legged adult after four moultings. Some of the cases of "blackheads" are due to this face mite, and from 50 to 90 per cent of human beings have been reported to harbor them (Germany). Statistics do not show greater frequency of mites in comedones in the U. S. than in normal glands. They do not seem to cause any ill effects in man, but the comedone continues until the mite is expelled. A different species causes a severe mange in dogs.

Tarsonemidae (Louse Mites)

This acarine family shows a complete dimorphism. The last two pairs of legs are widely separated from the front legs. The *Pediculoides ventricosus* is oval; the male is about 125 × 75μ and has claws at the extremities of the anterior and posterior pairs of legs; the two other pairs have hooklets and a sucking disc. The female is about twice as long but of the same breadth as the male, and has claws only on the anterior legs. The chelicerae are lancet-shaped and retractile. The large pedipalps are fused together anteriorly. The gravid female is like a ball and is about 1000μ in diameter.

These mites are viviparous, a single female containing from 200 to 300 sexually mature mites. They live on various insect larvae found on cereals and other plants—particularly straw and cotton, and from handling, or sleeping on infested bedding material, man may contract a violent dermatitis, possibly covering the entire body. The eruption with wheals, papules and vesicles appears in about 15 hours—marked itching and burning and sometimes fever.

Ixodoidea (Ticks)

The superfamily Ixodoidea is of great importance medically. It is divided into 2 family groups the Argasidae and the Ixodidae. The former is discussed in Chapter VII (African tick fever).

Family Ixodidae.—Mouth parts project in front of body when viewed dorsally. Scutum present. Stigmal plates posterior to fourth pair of legs. Adults have suckers beneath claws. Skin finely striated.

Anus behind middle of venter. Sexual dimorphism marked. Male has well developed scutum; female has porose areas.

Section Ixodeae (Prostriata).—Transverse recurved preanal groove in female. Male has ventral surface covered with chitinous plates. No eyes. Genus *Ixodes*.

Ixodes has long rostrum with slender palpi—palpi narrow at base, leaving gap between them and hypostome. No festoons.

I. ricinus is the intermediate host of *Babesia bovis*, the cause of cattle fever of Europe. This and other species may cause tick paralysis.

Section Rhipicephalae (Metastriata).—Anal grooves behind the anus or absent in the female. Ventral surface of male without adanal plates (in *Dermacentor*, *Haemaphysalis*, *Aponomma* and *Amblyomma*) or with one or two pairs (in *Hyalomma*, *Rhipicephalus* and *Boophilus*). Marginal festoons present, more distinct in the males.

The more important genera can be distinguished as follows:

1. Palpi long and slender 2
   Palpi short 3
2. Segments of palpi equal in length. Eyes present .... *Hyalomma*
   Second palpal segment much the longer 4
4. Very ornate. Eyes present .... *Amblyomma*
   Not ornate. Eyes absent .... *Aponomma*

3. Eyes absent. Palpi conical. Rostrum broad. Not ornate........*Haemaphysalis*
Eyes present. Palpi not conical 5
5. Anal grooves absent. Palpi have sharp transverse ridges. Not ornate....*Boophilus*
Anal grooves present, distinct 6
6. Ornate. Square rostrum. Second and third joints of palpi as broad as long...... *Dermacentor*
Not ornate. Rostrum hexagonal dorsally........................*Rhipicephalus*

A further description of ticks and their classification is also discussed in Chapter VII, the tropical relapsing fevers, where species of the genus *Ornithodorus* have been particularly considered, in the transmission of African tick fever.

Dermacentor andersoni (*D. venustus*) Fig. 218 has been referred to and illustrated in the chapter on the transmission of spotted fever of the Rocky Mountains. It is a reddish brown tick with a dorsal shield marked by black and silvery-white lines.

The male is about 2.5 by 4 mm. The young female is about 6 by 2.4 mm.; when replete, 15 by 9 mm. It occurs in the northwestern United States and British Columbia, where it is the vector of Rocky Mountain spotted fever. It transmits tularaemia and is a cause of tick paralysis. It appears to be gradually extending its range. The larvae and nymphs utilize small rodents as hosts, but the adult ticks require large mammals or man. The tick survives long periods of starvation. According to Cooley if the adult fails to find a host the first season it will hibernate and try again the second year; if necessary, again the third year; and rarely may survive to try again the fourth year.

D. variabilis, the common dog tick of North America, is the vector of spotted fever in the eastern United States. It also transmits tularaemia. Other ticks which have been shown to convey rickettsial diseases are *Amblyomma cajennense* in Brazil, *A. hebraeum Rhipicephalus appendiculatus* and *Boophilus appendiculatus* in South Africa, and *Rhipicephalus sanguineus* in Europe. *Boophilus annulatus* transmits *Babesia bigemina*, the cause of Texas fever of cattle. Larvae developing from eggs of female ticks which have fed on infected cattle transmit the disease. Several species of *Rhipicephalus* have been shown to transmit other piroplasmoses to various species of mammals. *Haemaphysalis leporis-palustris*, the common rabbit tick, disseminates Rocky Mountain spotted fever and tularaemia among rodents, but rarely if ever conveys them directly to man. Anigstein and Bader (1942) report that *Amblyomma americanum* probably transmits endemie typhus. Parker, Philip and Jellison have found it an efficient carrier of Rocky Mountain Spotted Fever.

It has been shown that several species of ticks will harbor the virus of yellow fever for from 4 to 28 days, and experimental transmission to monkeys has been reported to follow the bite of *Ornithodorus rostratus*, *O. moubata*, and *Amblyomma cajennense* 4 to 8 days after infection (Aragao, 1933). There is no evidence as yet of transmission by ticks under natural conditions.

Tick paralysis is an acute intoxication which is caused by the bites of rapidly engorging female ticks of certain species. It has been observed chiefly in sheep, dogs, and occasionally in children. It is most apt to occur if the bite is about the head or neck. It is characterized by fever and an acute ascending paralysis (beginning in the legs) which might be confused with poliomyelitis. If the tick is discovered and removed promptly, recovery occurs in a few days. If this is not done, death may occur from paralysis of the respiration. It is believed to be caused by a venom secreted by the salivary glands of the tick during the period of rapid egg development. It has been reported chiefly from Oregon and British Columbia (where it is caused by *Dermacentor andersoni*), and also from portions of Europe, South Africa and Australia, where species of *Ixodes* have been incriminated.

Barnett (1937), Gibbes (1938) and Mail (1939) have reported with reference to wood tick paralysis in the United States due especially to *Dermacentor andersoni*. In one case reported by Robinow and Carroll (1938), from Georgia, and one by Beach and Ravenel (1941) in South Carolina, the tick was *D. variabilis*. In British Columbia it is said some 150 cases, many of them fatal, are reported every year.

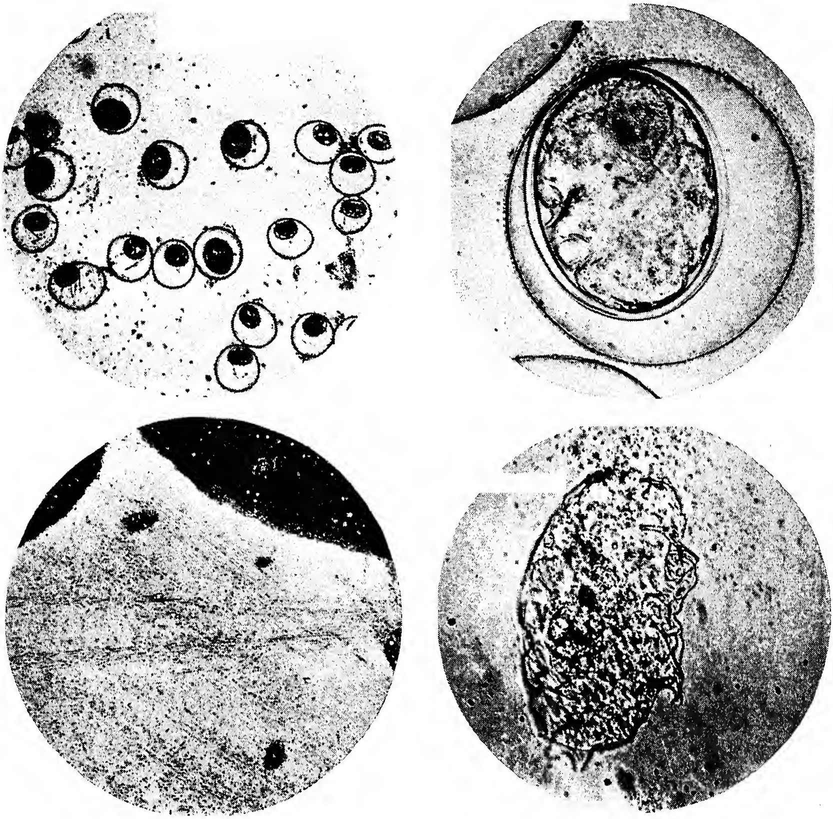

FIG. 360.—Development of *Porocephalus*. (After van den Berghe.)
1. Ova in the pulmonary mucus of *Boa constrictor*.
2. The ovum more strongly magnified.
3. To the left and below, two larvae of *Porocephalus clavatus* living between the folds of the mesentery in an experimentally infected rat, 6 days after ingestion of the ova.
4. One of the larvae more highly magnified.

LINGUATULIDA (PENTASTOMIDA) (THE TONGUE WORMS)

These are degenerate, worm-like arthropods formerly classified with the Arachnida, although they are not closely related to any other group. The adults have elongated annulated bodies. They have two pairs of retractile mouth hooks. Otherwise there are no traces of legs, antennae or palpi in the adults. The species of medical interest are included in the family Linguatulidae (*tongue worms*).

Linguatula serrata Fig. 359 (*L. rhinaria*) in the adult stage is usually a parasite of dogs or other carnivores (rarely of man), occurring in the nose or paranasal sinuses where it causes severe chronic inflammation and bleeding. The male is white, 2 cm.

long; the female yellowish, 10 cm. long and has about 90 annular "segments." The eggs are thick-walled, contain a developed embryo, and are enclosed in a thin-walled bladder-like structure containing fluid. These are discharged with the nasal secretions. When ingested by a suitable intermediate host, usually a herbivore, occasionally man, a minute (75μ) four-legged larva is liberated. This penetrates through the gut wall and reaches usually the liver of mesenteric glands where it develops, moulting several times and finally (after 6 months) encysts as a nymph. This is about 5 mm. long and resembles the adults except that there is a row of minute spines on the posterior margin of each ring. When the intermediate host is eaten the nymphs make their way to the sinuses and develop into adults.

The parasite is widely distributed but nowhere abundant. Human infection with adult parasites is very rare, but infection with the larvae is not uncommon in parts of Europe. Diagnosis intravitam is rarely possible. Little is known as to symptomatology.

Armillifer armillatus is a parasite living in the trachea and lungs of pythons and other African snakes. Other species are found on the surface of the liver sometimes encysted. The males are 3 to 5 cm. long with about 16 rings; the females 3 to 12 cm. long with about 20 rings. The eggs (80 to 100μ) contain a developed larva. They are passed with the bronchial secretions of the snakes and are ingested with contaminated food or water by monkeys, occasionally by various hervibores or by man. The larvae penetrate into the liver or other organs, undergo a protracted period of development (1 to 2 years) and finally encyst (nymph). When the intermediate host is eaten by a snake the nymphs are liberated and penetrate into the lungs where they develop rapidly into adult forms. Many cases of human infection have been reported from west Africa, especially the Belgian Congo. A few cases of human infection have been reported from the Orient (with *A. moniliformis*) and two cases from America (possibly with *Porocephalus crotali* of rattle snakes).

It has been suggested that human infestations were probably acquired from ingesting raw infected snakes. However, this seems somewhat improbable. Moreover, Van den Berghe (1938) in experimental infections in animals, has shown that man is probably infected by drinking water containing the ova deposited from either the sputum or excreta of the snake. In water, the ova showed considerable resistance. The envelope of the egg does not become digested in the gastric juice, but in the duodenal juice. The larvae then penetrate the intestinal wall and the layers of the peritoneum and enter either the thoracic or abdominal organs, as the lungs and liver.

The Insects in Relation to Disease

Insecta

The class Insecta has one pair of antennae, three pairs of mouth parts (the fused labium being considered as one pair), and three pairs of legs. They have three divisions of the body—head, thorax, and abdomen.

The head carries the antennae and mouth parts; the thorax, which is divided into the prothorax, mesothorax and metathorax, carries upon the ventral surface of each thoracic segment a pair of legs and on the dorsal surfaces of the two posterior segments a pair of wings. The abdomen does not support appendages. The air is supplied by means of tracheae—branching breathing tubes which have external openings or stigmata. The tracheae are stiffened by spiral chitinous bands. The Malpighian tubules are excretory organs of the alimentary system and excrete nitrogenous waste material. Insects have two pairs of wings, the second pair of which is frequently rudimentary and shows simply as knob-like projections. These are termed halteres or balancers. In some insects both pairs of wings are rudimentary, as in Siphonaptera.

Classification of the Class Insecta

Order	Family	Sub-family	Tribe	Genus	Species
Anoplura	Pediculidae			Pediculus	P. humanus var. humanu
					P. humanus var. corporis
				Phthirus	P. pubis
Hemiptera	Cimicidæ			Cimex	C. lectularius
					C. rotundatus
	Reduviidae			Triatoma	T. megista
					T. sanguisuga
Siphonaptera	Pulicidae			Pulex	P. irritans
				Xenopsylla	X. cheopis
	Archaropsyllidae			Ctenocephalus	C. canis
					C. felis
	Histrichopsyllidae			Leptopsylla	L. musculi
	Dolichopsyllidae			Ceratophyllus	C. fasciatus
				Hoplopsyllus	H. anomalus
	Tungidae			Tunga	T. penetrans
Diptera	Tabanidae			Tabanus	T. glaucapis
				Haematopota	H. pluvialis
				Pangonius	P. beckeri
				Chrysops	C. discalis
					C. dimidiatus
	Oscinidae			Hippelates	H. pallipes
	Muscidae			Glossina	G. palpalis
					G. morsitans
				Stomoxys	S. calcitrans
				Musca	M. domestica
				Auchmeromyia	A. luteola
				Fannia	F. canicularis
				Calliphora	C. vomitoria
				Lucilia	L. caesar
					L. sericata
				Phormia	P. regina
				Cochliomyia	C. americana
				Chrysomyia	C. macellaria
				Cordylobia	C. anthropophaga
	Sarcophagidae			Sarcophaga	S. carnaria
				Wohlfahrtia	W. vigil
	Oestridae			Dermatobia	D. hominis
				Hypoderma	H. bovis
				Gasterophilus	G. nasalis
	Simuliidae			Simulium	S. damnosum
				Eusimulium	E. metallicum
	Psychodidae			Phlebotomus	P. papatasii
					P. argentipes
	Chironomidae			Culicoides	C. furens
	Culicidae	Culicinae	Sabethini	Wyeomyia	W. smithii
			Culicini	Aedes	A. aegypti
				Culex	C. quinquefasciatus
			Anophelini	Anopheles	A. maculipennis
		Corethrinae		Corethra	C. cinctipes

When insects show metamorphosis voracious worm-like larvae hatch from eggs; these larvae are succeeded by a quiescent non-feeding encased pupa which finally develops into an imago or fully developed insect. An insect which does not present this developmental cycle shows incomplete metamorphosis. Of the class Insecta only the Anoplura, Hemiptera, Siphonaptera, and Diptera are of special importance.

Anoplura (Siphunculata)

These are small dorso-ventrally flattened wingless insects not showing metamorphosis.

Pediculidae

In this family there are no wings and there is no metamorphosis. They have simple eyes and 5 joints to the antennae. The legs are well developed and terminate in powerful claws. The young resemble the adults. The ovoidal, operculate eggs (nits) are deposited on hairs or clothing of the host.

Pediculus Humanus Var. Corporis (*P. vestimenti*). Figs. 210 and 361.—This louse lives about the neck and trunk underclothing, being rarely found on the skin. The louse feeds about twice a day, deprivation of food causes the death of the adult in 9 days and the newly hatched louse in two days.

Pediculus Humanus Var. Capitis.—The eggs, usually 60 in number, are deposited on the hairs of the head, the favorite region being back of the ears. They hatch out in 6 days. The lice larvae on emergence closely resemble the adult and begin to feed shortly after hatching. They moult about every 3 days and become adults within 10 days.

These organisms have been discussed and described in the chapters on Typhus and Relapsing fevers.

FIG. 361.—Female *Pediculus humanus*, var. *corporis*. (Schamberg.)

The body louse (and probably the head louse) has been shown to transmit epidemic typhus fever and trench fever. Mackie (in India) and Nicolle (in northern Africa) showed that it is a vector of some strains of relapsing fever (in Europe, India, China, northern Africa and North America). Whereas the louse can transmit typhus and trench fever by biting, the spirochaetes are introduced only by scratching and rubbing the infective body fluids of the louse into the wound. Typhus and trench fever are usually introduced in the same way, either the crushed body of the louse or especially the faeces being infectious. These viruses apparently undergo some developmental cycle in the louse, since the louse is incapable of transmitting these diseases until several days have elapsed after the infecting feeding: typhus fever, 8 to 10 days (the faeces may be infectious after 3 or 4 days); relapsing fever, 4 days; trench fever, faeces infective after 7 days.

Phthirus Pubis.—This louse is popularly known as the crab louse. The female is little more than 1/25 inch in length, and the male a trifle less. They are almost square. The second and third pair of legs are supplied with formidable hooks. They have a preference for the white race and live about the pubic region. The female lays about a dozen eggs, which hatch out in about a week. It is not known to be a vector of any infection.

The rat louse, *Polyplax spinulosus*, is important as a vector of endemic typhus among rats. The rabbit louse, *Haemodipsus ventricosus*, was shown by Francis to be a vector of tularaemia among rabbits. The dog louse (*Trichodectes canis*) is one intermediate host of *Dipylidium*.

HEMIPTERA (RHYNCHOTA)

The Hemiptera or bugs are insects possessing mouth-parts modified for sucking in which the lower lip or labium or beak, having 3 to 4 seg-

ments, has its edges curved to form a groove. Within this groove are the biting parts—the bristle-like mandibles and maxillae.

The former are double grooved on their internal surfaces and thus when apposed form two tubes, one for injection of saliva and the other for suction of juice or blood. The maxillae support the mandibles. When in repose the beak or rostrum is bent back under the head or thorax. The beak is covered by the labrum only at its base, thus differing from the Diptera in which the labrum goes into formation of the sucking tube.

Bugs have no palpi. They have two pairs of wings which in some genera, however, are rudimentary. The metamorphosis in this order is incomplete.

Cimicidae

These have a flattened body, a three-jointed rostrum, and four-jointed antennae. Their wings are atrophied.

Cimex Lectularius (*Acanthia lectularia*) (Fig. 74, p. 330).—This is the cosmopolitan bedbug or chinch. It measures about 1/5 by 1/8 inch (5 by 3 mm.). It is brownish-red in color. The most conspicuous feature of the bedbug is the long proboscis continuous with the dorsal integument of the head and tucked under the ventral surface. In biting the proboscis is straightened out and 4 piercing stylets are protruded to puncture the skin. There are two prominent eyes and two four-jointed antennae. The prothorax is flattened at the side. There are eight abdominal segments. The bedbug lives in cracks and crevices, especially about beds. It is said they can migrate from house to house. It is evident that they have been frequently transferred with soiled clothes. They have a penetrating odor when crushed. The female deposits about 50 eggs at a time in cracks and in 10 days they hatch out into larvae which pass insensibly into adults by a series of 5 moultings during a period of 2 or 3 months. The depositing of eggs occurs about 4 times a year. The larvae bite as well as the adults. The average period of active life is probably from 3 to 6 months, but in a cool place they may survive a year without food. They will also bite other animals and occasionally infest chicken coops and laboratory animal cages. They are easily killed by moderately high temperatures (110° to 120°F.).

Cimex Rotundatus (*A. rotundata*).—In India the *C. rotundatus* is the one encountered. It is dark mahogany in color, has a smaller head, narrower abdomen, thick rounded prothoracic borders and is more densely covered with hairs than *C. lectularius*.

Related species of bugs parasitic on other animals, particularly bats and birds, occasionally attack man, but they rarely establish themselves in human habitations.

Relation to Disease.—The bedbug has been suspected of being a transmitter of many different infections, but there is no convincing evidence that it plays a really important part in the natural transmission of any of them. Francis showed that it is readily infected with *P. tularensis* and transmits the infection by biting (mice). It can be infected with plague bacilli, and animals can be infected by rubbing the crushed bug or its faeces into the skin, but not by a bite. The same appears to be true of *Borrelia recurrentis*, *Leptospira ictero-haemorrhagiae* and *Trypanosoma cruzi*. It probably plays no part in the spread of typhus fever or *Leishmania* infections. The ordinary pathogenic bacteria do not multiply in the bug because of the bactericidal action of the contents of its digestive tract.

Reduviidae

These hemiptera are popularly known as assassin bugs, corsairs, or kissing bugs. They have a long narrow head and a distinct neck. They are vigorous fliers and run-

ners. The majority are predacious, feeding on other insects, but if disturbed may inflict very painful bites on man. A few have become blood-sucking parasites, and are of great medical importance because several species are hosts of the South American trypanosome, *T. cruzi*. The parasite undergoes a regular cycle of development in the bug and is transmitted by it. (See section on Trypanosomiasis.) These species are nocturnal biters, and their bites are relatively painless. They are common in tropical America.

Triatoma megista (*Conorhinus megistus*) (Figs. 48 & 210, pp. 211 & 935) is the important vector in Brazil. It is called "barbeiro" because of its preference for biting the face. It is black with red markings on the wings, abdomen and prothorax. The antennae (in this genus) are inserted midway between the eyes and the point of the head. The bugs live in the native huts, hiding in cracks during the day and feeding on the inmates at night. Its habits are like those of the bed bug. The wingless larvae (which also bite) hatch out of the eggs in about a month and attain maturity in about a year. The infection is spread among the bugs by their habit, when opportunity offers, of sucking blood from the distended abdomens of their companions, and (in *Rhodnius*) by the coprophagous habits of the larvae.

Triatoma infestans replaces the preceding species as a vector from southern Brazil southward and westward through Chili, Bolivia and Argentina. Other species naturally infected include *T. braziliensis*, *T. dimidiata*, *T. geniculata*, *T. rubrovaria* and *T. sordida*.

Rhodnius prolixus (and *R. pictipes*) replaces *Triatoma* as the principal vector in northern South America. It is brown with yellowish markings. The antennae in this genus are inserted near the extremity of the head.

Several species occur in the southwestern United States, including:

Triatoma sanguisuga (*Conorhinus sanguisugus*) the Texas or Mexican "bedbug." It sometimes preys on and obtains its blood from the common bedbug (*Cimex*) and perhaps thus having acquired a taste for human blood it now attacks man. It is nearly an inch long, dark brown in color, with a long flat narrow head and a short thick rostrum. It is spreading northward. It has been infected with *T. cruzi* experimentally.

Siphonaptera

The fleas are laterally flattened, markedly chitinized, wingless insects which undergo a complete metamorphosis. The classification of the Siphonaptera and the importance of the Pulicidae in the transmission of disease has already been discussed in Chapter XVIII (Plague).

As a result of the convincing experiments of the Indian Plague Commission, the role of fleas in the transmission of plague was absolutely established. It is by the bite of *Xenopsylla cheopis* that plague is chiefly transmitted from rat to rat, and in bubonic and septicaemic plague it is apparently the intermediary in human infection. However any species of flea which lives on the rat is capable of transmitting plague, as would also *Pulex irritans* if fed on the blood of a human case of septicaemic plague.

Trypanosoma lewisi (and possibly other rodent trypanosomes) also are transmitted by fleas, either *Pulex irritans* or *Ctenocephalus canis*. The trypanosome undergoes development in the flea, the infecting material is in the faeces of the flea, and transmission may occur by the licking on the part of the rat, of faeces from an infected flea. The infection has no connection with the puncture wound of the flea as is the case with plague.

The rat fleas (*X. cheopis* and *C. fasciatus*) also serve as vectors of endemic typhus (*Rickettsia mooseri*), conveying the organisms from rat to rat and rat to man. (See Chapter XXV.) Fleas may convey tularaemia

from rodent to rodent but are not known to have infected man. The evidence at present indicates that they are not concerned with the transmission of the trypanosome diseases of man or the larger mammals, or of *Leishmania*.

TUNGIDAE

In the TUNGIDAE family of fleas, the abdomen of the female becomes enormously distended with eggs, and she remains fixed in the burrow she has made under the skin, whereas in all other families the female remains practically unchanged with freedom of movement after fecundation.

Tunga penetrans (*Dermatophilus penetrans*), the jigger, chigoe, nigua (of South America) or sandflea, is of great importance in a number of tropical countries. Originally found in tropical America, it was said to have been introduced into Africa in sand ballast in 1872. It spread rapidly over nearly the whole of Africa. However, the affection has apparently not yet established itself in India or in Europe, although a closely related species, *T. caecigena*, has been found on the ears of rats in Shanghai.

The male and virgin female are relatively unimportant as they do not penetrate the skin but act as ordinary fleas. The female, which when unimpregnated is only about 1/24 inch long, when impregnated bores its way into the skin of man, especially about the toes, soles of the feet or finger-nails, and in the chosen site develops enormously, becoming as large as a small pea. This enlargement takes place in the second and third abdominal segments which are packed with eggs measuring about 400μ long and numbering about 100. Clinically a small black spot in the center of a tense, rather pale area is characteristic. The metamorphosis is similar to that of the flea. *Tunga* can be differentiated by the proportionately larger head, and especially by the fact that the head has the shape of the head of a fish, distinctly pointed. With the fleas the lower border of the head comes out in a straight line to join the curve of the upper part. In the *Tunga* lower and upper border of head are both curved.

Man and pigs seem to be the principal hosts, but cats, dogs and rats are also affected.

The wounds made by the burrowing female in the skin may become much inflamed and very painful. Frequently the distended abdomen of the flea is crushed and the eggs released in the wound, and in such cases marked inflammation may occur unless the crushed body and eggs are immediately expelled. When the eggs are laid in the skin, the tissues around them ulcerate and pus is formed. In this way, the contracted female flea is expelled. The lesion which is left is very liable to infection by bacteria, and this has sometimes resulted in the loss of toes or larger parts of the limbs through blood poisoning. In Central America, deaths from tetanus and from gas gangrene following chigger wounds have not infrequently been reported. Quiros has estimated that 250 deaths from tetanus occurred in Costa Rica in 4 years from infection of "Nigua" (sand flea) wounds. While sometimes only a few fleas are present at the time, there are cases in which hundreds infest a person at once. Then the skin may become honeycombed and the foot or other parts of the body become so sore that the patient is temporarily incapacitated.

The *treatment* formerly recommended was the destruction of the fleas while imbedded in the wounds by applying insecticides, the dead insect being later removed after ulceration, often with the needle. It is now recommended that the entrance hole of the flea be first enlarged with a

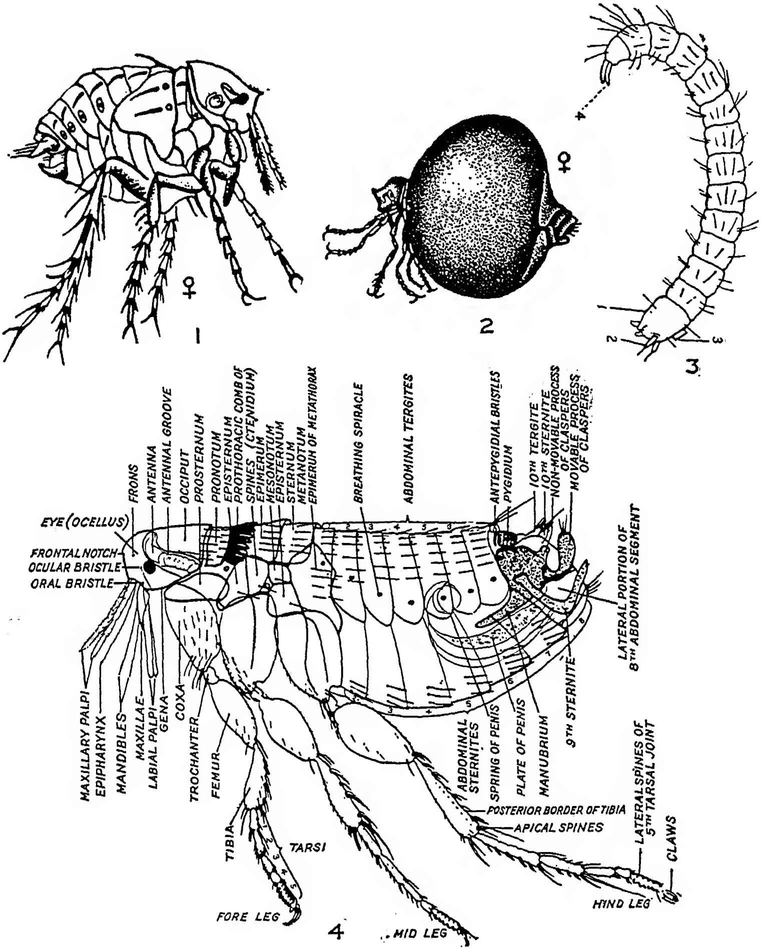

FIG. 362.—1–2. *Tunga penetrans.* (1) Adult; (2) egg-distended female. 3. Flea larva highly magnified. (1) Head; (2) antennae; (3) egg-breaker; (4) caudal stylets. (From Byam and Archibald.) 4. External anatomy of a flea. (After Fox.)

clean needle and the parasite removed entirely. Then the wound should be cleansed with an antiseptic solution and dressed with an antiseptic ointment.

Quiros, in Central America, has employed 2½ grams of salicylic acid and 10 grams of ichthyol in 10 grams of vaseline. This is rubbed into the bite every 3 days, especially after bathing, and expells newly attached fleas and prevents fresh infections. For prevention, thorough rubbing of the foot every 2 or 3 days with vaseline 3½ oz. and 15

FIG. 363.—Camera lucida drawing of section through lesions containing Tunga (Dermatophilus) penetrans. (A Hamilton Rice—Harvard Amazon Report.)

FIG. 364.

FIG. 365.

FIG. 364.—Sand-flea female; much enlarged.

FIG. 365.—Sand-flea female. Shortly after penetrating the skin. The anterior part of the abdomen is much more distended than the posterior; the enlarged part is disk-shaped, not globular. (From Mense.)

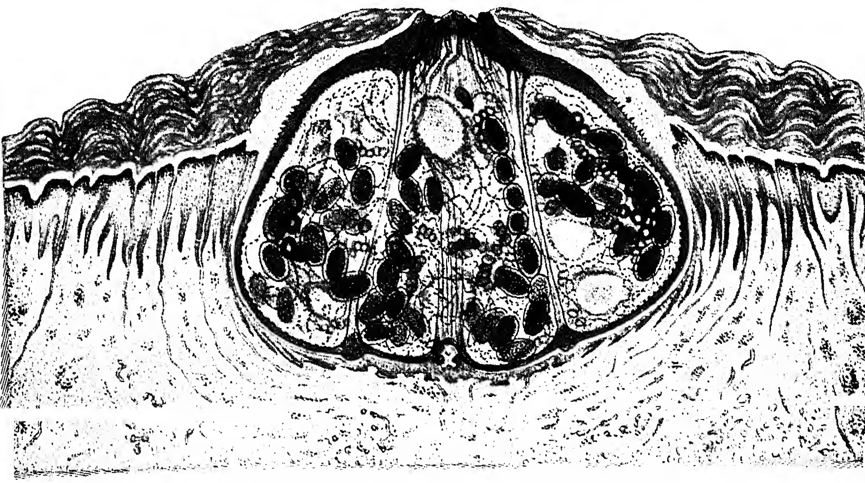

FIG. 366.—Sand-flea in sole of foot of a negro. Section greatly enlarged. (After Fülleborn.)

drops of lysol or cresol soap, has been employed. Infection can be avoided to a great extent by the use of high boots or shoes and leggings. In Central America, Quiros recommended that the driving of hogs affected with jiggers through the streets should be prohibited, together with regulations for treatment of the affected hogs.

The "sticktight" flea, *Echidnophaga gallinacea*, is classified in another family, ECHIDNOPHAGIDAE. It is a small, dark colored flea which commonly attacks chickens in tropical and subtropical countries, including the southern United States. However, while the normal host is the chicken, other poultry, dogs, cats, rabbits, rats and other animals besides man are attacked. In human beings it can easily be found and removed, as it is not as active as the *Tunga* flea.

Prevention.—Strict cleanliness in private houses or public buildings prevents fleas from breeding in them. Dusty cracks, uncared for carpets, etc., furnish excellent breeding grounds for the human flea. An infested house can be rid of fleas, except the eggs, by sprinkling the floors with naphthalene and closing up the rooms every night, or by scattering sodium fluoride or pyrethrum powder on the floors, especially with a dust gun, or spraying with pyrethrum insecticide. Rat fleas, of course, can be controlled only by the control of the hosts. (See Plague disinfection, Ch. XVIII.)

DIPTERA

The insects of the order Diptera are of great importance medically, either because of the direct irritation of their bites, because of their transmitting disease directly, as does the common house fly typhoid fever, or because of acting as intermediate or definitive hosts for various parasites. They are characterized by mouth parts formed for puncturing, sucking, or licking. They present a complete metamorphosis, larva, pupa, and imago. As a rule, the Diptera have one pair of functional wings, the second pair being modified into halteres.

The anterior portion of the head, which lies below the origin of the antennae, is the face, and on each side of the face are seen the cheeks which should be studied as to presence or abundance of hairs. The antennae which separate the frons from the face are of great importance in classification. In the Muscidae the appearance of a feathery structure, projecting from the terminal segment of the antennae, and called the *arista*, is important. This may be bare or feathered, and the feathering may be only on one side or of one part.

The males of flies in which the two compound eyes come together above the antennae are referred to as holoptic; if more or less widely separated, as dichoptic. Ocelli are single eyes, usually three in number, and, when present, situated in the triangular space between the compound eyes in the frons (the space separating the compound eyes).

In studying the biting flies it is very important to recognize the anterior, small, or mid-cross vein in the wings. This short transverse rib or vein is the key to wing venation. Beneath it is the discal cell, and it bounds the first posterior cell internally or basally. The fourth longitudinal vein, which touches the bottom of the mid-cross vein, is of particular importance as it gives different shapes to the first posterior cell as it runs along the lower border of this cell. The closed-in discal cell is below the fourth longitudinal vein. The character of the antennae should also be noted carefully. The study of the bristles about head, thorax, and abdomen (chaetotaxy) is more difficult. Anyone taking up the study of flies should note carefully the wings, etc., of *Musca domestica*. By putting a few house flies on moist horse manure in a gauze-covered bottle the entire metamorphosis may be observed.

CLASSIFICATION OF DIPTERA

I. Suborder Orthorrhapha. The larvae have a well-differentiated head. Pupa naked. Imago escapes from the pupal case through a T-shaped break on the dorsum near the anterior end. No frontal lunule. Wing venation simple.

a. Series 1. Nematocera. Midge-like insects with long many-jointed (8 to 16) antennae and usually long slender palpi of one to five segments. Anal cell not narrowed toward the wing margin.

α. Marginal vein not continued beyond the tip of the wing.

1. Simuliidae. (Buffalo gnats, black flies). Antennae shorter than the thorax, with 11 segments, not plumose. Wings broad, without scales or hairs.
2. Chironomidae: (Midges). Antennae longer than the thorax, bushy, with 14 segments. Wings narrower, median vein forked. Wings bear setae, no scales.

β. Marginal vein extends entirely around the wing. Second and fourth longitudinal veins forked.

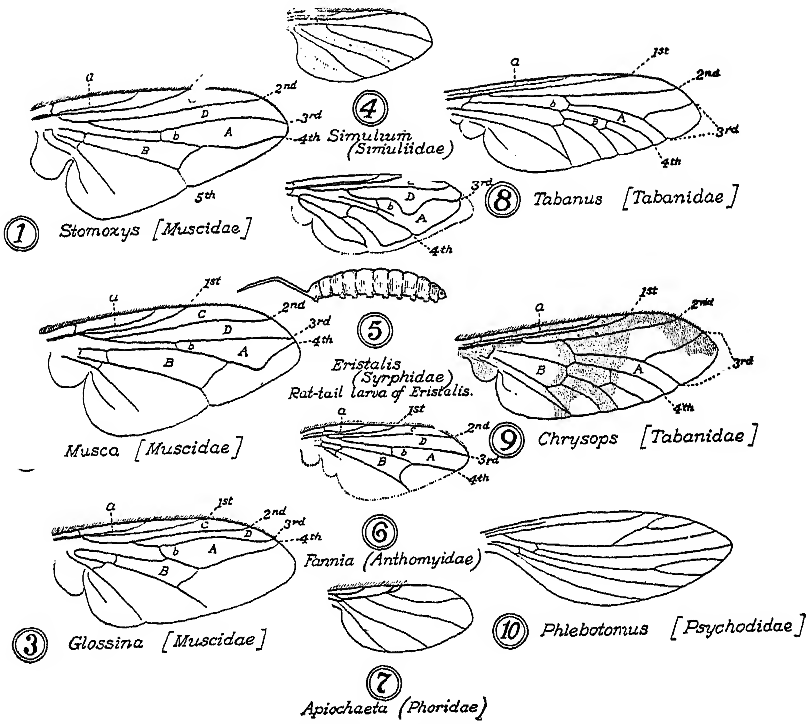

FIG. 367.—Wing venation of Diptera. *A*, First posterior cell; *B*, discal cell; *b*, mid-cross vein; *a*, auxiliary vein; *C*, marginal cell; *D*, submarginal cell.

3. Psychodidae (Moth midges, sand flies). Wings and body thickly covered with coarse hairs. Wings ovate or pointed.
4. Culicidae (Mosquitoes). Without these characters. Wings with rounded tips. Posterior margin and veins of wings fringed with scales. Mouth parts long, slender, adapted for biting.

b. Series 2: Brachycera. The antennae are short, composed of only two or three simple joints, with or without a style or arista. The palps are nearly always short and never more than two-jointed. Anal cell closed or narrowed toward the margin of the wing.

Tabanidae (Horse flies). Third joint of antennae complex. Costal vein surrounds the wing.

II. Suborder Cyclorrhapha. Head of larvae not differentiated. Pupa enclosed in last larval skin. Imago escapes through an anterior circular opening in the puparium pushed open by the ptilinum. (This is an inflatable organ projecting just above the root of the antennae and is retracted as soon as the imago escapes, leaving behind typical scars, the frontal lunule and the frontal or ptilinal suture) (see Fig. 368). Wing venation more complex.

a. Series 1. Aschiza. Ptilinum small, frontal suture absent.
 Family Syrphidae (Hover flies). Anal cell ends in an acute angle, reaching nearly to the wing margin. A spurious "vein" between the third and fourth longitudinal veins. (Mostly large, brightly colored flies. A few cases of human intestinal myiasis have been reported due to the "rat-tailed" larvae of *Eristalis*.)

b. Series 2. Schizophora. Ptilinum large; frontal suture and lunule marked, causing retraction of front of head. Head freely movable.
 α. Pupipara.
 Family Hippoboscidae. Blood-sucking ectoparasites of birds and mammals with tough leathery bodies, more or less developed wings and indistinctly segmented abdomens. The larvae are completely developed at birth. (A few species are vectors of disease; e.g., *Melophagus ovinus*, the sheep "tick" or ked, conveys sheep trypanosomiasis, and *Lynchia maura* is the definitive host of *Haemoproteus columbae* of pigeons. None are known to convey human infection.)
 β. Myodaria. Without these characters.
 Acalypterate myodaria have no scales covering the halteres.
 Oscinidae (Chloropidae), the eye flies.
 (Also includes the cheese fly, *Piophila casei* and other small flies, chiefly of minor medical interest.)
 Calypterate Myodaria have large scales (squamae) covering and concealing the halteres. (Includes a very large number of species, many of great medical importance.)
 1. Oestridae (Bot flies). Mouth opening small, mouth parts rudimentary.
 2. Sarcophagidae (Flesh flies). Mouth parts normal, adapted for sucking. Arista of antennae plumose on proximal half only. Hypopleural bristles present.
 3. Muscidae (Large family). Mouth parts adapted for sucking or biting. Arista of antennae plumose to the tip.

Tabanidae

This family includes the deer-flies, horseflies, gadflies, breeze flies or green-headed flies. It is one of the most numerous families of the Diptera—there being nearly 2500 species. The females are mostly blood-suckers; the males live on flowers and plant juices. The eyes are usually large, very brilliant in color, and in the male make up the greater part of the head.

They belong to the suborder Orthorrhapha and in the group of short-antennae flies (Brachycera). The wings are large and encircled by the costal vein. The third longitudinal vein is forked. The fourth longitudinal vein breaks up three times thus enclosing the discal cell. Five posterior cells are always present. The squamae are large.

The antennae consist of three segments, the third of which is compound. No arista. The mouth parts are complete in the female. The epipharynx is tube-like, the hypopharynx has a groove and both are awl-shaped. The paired maxillae are serrated and the mandibles lancet-like. They have rather coarse maxillary palps. The labellae are prominent at the extremity of the fleshy labium. In the male the mandibles are atrophied. The Tabanidae are thick-set flies and rarely show color. The body of the larva has eleven segments and a small but distinct head. The eggs are deposited in masses on the leaves or stems of plants about marshy places. The larva is carnivorous. Of the numerous genera of Tabanidae the more important are:

Tabanus.—No ocelli. No spurs at tips of hind tibiae. The last (third) antennal segment is composed of five parts and shows a crescentic notch. Wings clear or smoky,

not spotted, do not overlap. A huge genus (over 1000 species), world wide in distribution, chiefly large powerful fliers which bite viciously both man and animals. *T. glaucopis* is the intermediate host of *Trypanosoma theileri*, a non-pathogenic parasite of cattle (Europe). Tabanids are suspected of being the vector of *Leishmania* in the forested regions of southern Brazil and Paraguay.

Haematopota.—There is no crescentic antennal notch, and the third antennal segment is composed of four parts. The wings overlap and show scroll-like markings. The abdomen is narrower than in Tabanus. No ocelli. Common in Africa and the Orient. The brimp, one of the Haematopota, bites man severely.

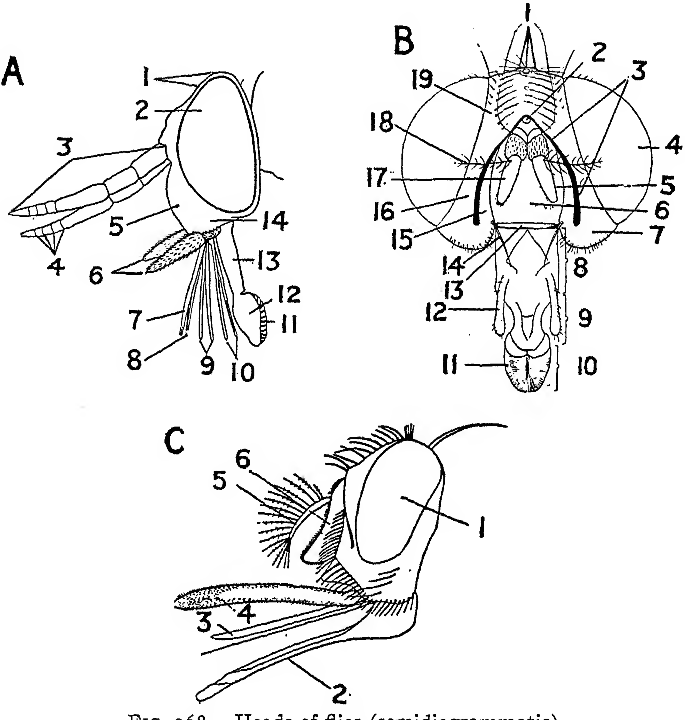

FIG. 368.—Heads of flies (semidiagrammatic).

A, Chrysops discalis. (1) Ocelli; (2) compound eye; (3) antennae; (4) annuli; (5) clypeus; (6) palpi; (7) labrum-epipharynx; (8) hypopharynx; (9) mandibles;'(10) maxillae; (11) pseudotracheal membrane; (12) labellae; (13) labium; (14) gena.

B, Muscoidean fly. (1) Ocelli; (2) lunula; (3) ptilinal suture; (4) compound eyes; (5) antennal grooves; (6) clypeus; (7) genae or cheeks; (8) rostrum; (9) haustellum; (10) labella; (11) pseudotracheal membrane; (12) palpi; (13) epistoma; (14) oral vibrissae; (15) facialia; (16) parafacials; (17) antennae; (18) arista; (19) parafrontals. (*After Fox.*)

C, Glossina sp. (1) Eye; (2) labium; (3) labrum; (4) palp; (5) arista; (6) antenna.

Pangonius is characterized by a very long, slender and more or less horizonta proboscis. The antennae are small. The third segment is composed of 7 or 8 parts. Wings clear or smoky.

Chrysops has three ocelli. The antennae are especially long and slender and have three segments, the last one of which is composed of five parts. The wings are widely separated and have a dark band along the anterior margin and a broad dark cross band one third removed from the tip. They inflict painful bites. There are many species, distributed throughout the world. *C. dimidiata* and *C. silacea* serve as intermediate hosts of *Loa loa* (tropical Africa).

Many species of tabanids may act as mechanical conveyors of infection although the organisms do not develop or multiply in the fly. This has been proved in the case of anthrax, e.g., and is of practical importance in numerous trypanosome infections, including *T. evansi*, *T. brucei*, *T. equinum* and *T. equiperdum*. It is essential that the first feeding of the fly

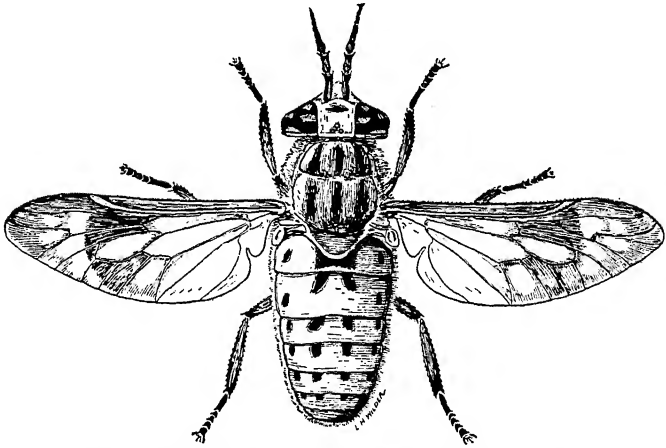

FIG 369.—*Chrysops discalis*, showing the characteristic non-pigmented discal cell whence is derived its name.

on an infected animal be interrupted and that the fly bite a second animal within about ten minutes.

Chrysops discalis, the western deer fly, was shown by Francis and Mayne (1921) to convey *Pasteurella tularensis* (in this way), both to man and animals, though the fly may remain infective for at least two weeks.

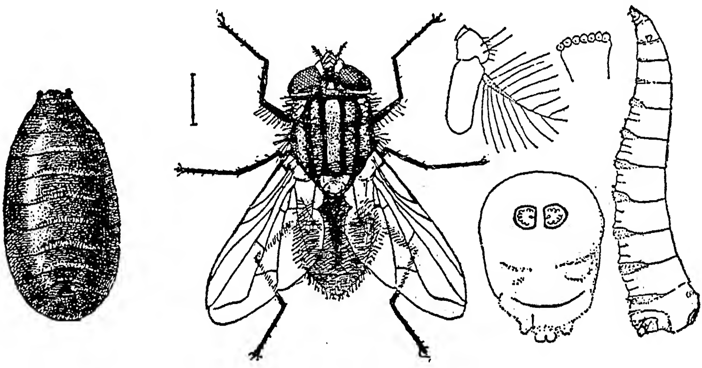

FIG. 370.—Common housefly (*Musca domestica*): Puparium at left; adult next, larva and enlarged parts at right. All enlarged. (From circular 71 (by L. O. Howard), Bureau of Entomology, U. S. Department of Agriculture.)

Oscinidae

The "eye" flies which belong to the acalypterate Myodaria are small hairless flies about 2 mm. long. They usually occur in swarms and cause annoyance by flying into

the eyes or ears or crawling over open wounds or ulcers to lap up secretions. Their habits are similar to those of the house fly, including that of regurgitating the contents of the oesophageal diverticulum while feeding ("vomit drop"). *Hippelates pusio* (in California and elsewhere) has been shown to spread "pink eye" and other infectious forms of conjunctivitis in this way. Krumm and Turner (1936) in Jamaica have demonstrated that *H. pallipes*, after feeding on open yaws ulcers, contains many motile spirochaetes in the oesophagus for several hours, and they have produced yaws lesions in rabbits by allowing infected flies to feed on open skin wounds.

Muscoidea

Under this heading we may group the Muscidae, Sarcophagidae and Oestridae which are calypterate Schizophora.

Muscidae

In the Muscidae the antennae hang down in front of the head in three segments and have an arista plumose to the tip on one or both sides. The first posterior cell is narrowed, due to bending up of 4th vein. There are no bristles on abdomen except at tip.

Adult Muscid Flies That Do Not Suck Blood.—In a majority of the Muscidae the proboscis is relatively short and stout with fleshy labella, and is adapted to licking or rasping but not to biting. (The maxillae and mandibles are atrophied, even in the biters.) These flies are important medically because, as a result of their filthy habits of eating and breeding, they often convey infection mechanically, and because the larvae of some of them cause myiasis. The more important genera are given in the following key:

Hypopleural bristles absent.
  Sixth vein short; fourth vein straight. . . . . *Fannia*
  Sixth vein longer; fourth vein angled at the distal end. Color opaque greyish-black. . . . . *Musca*
Hypopleural bristles present.
  Color greenish or bluish black.
    Basal section of first vein ciliated.
      Face yellow; one posthumeral bristle. . . . . (*Chrysomyia*) *Cochliomyia*
      Face black with black hairs; two posthumeral bristles. Prothoracic spiracle light orange. . . . . *Phormia*
    Basal section of first vein bare.
      Upper surface of lower squamae bare. . . . . *Lucilia*
      Upper surface of lower squamae pilose. . . . . *Calliphora*
  Color yellowish or reddish, non-metallic.
    Eyes of male approximated. Five or more ranges of setae on orbit. . . . *Cordylobia*
    Eyes widely separated. One seta on each orbit. . . . . *Auchmeromyia*

Musca Domestica.—The common housefly, *Musca domestica*, is the best example of this family.

The arista is feathered both dorsally and ventrally with straight hairs. The fourth longitudinal vein bends forward in a rather sharp angle as compared with *Stomoxys*, the first posterior cell of the latter having rather a fusiform appearance. The eyes are close together in the male, far apart in the female. In contrast to the other flies in this group *Musca* has no large bristle on the inner surface of tibia of the middle legs. The female lays about 125 eggs in a heap, preferably in fermenting horse manure. The larva comes out in about thirty-six hours. Very characteristic are the stigmata decorating the blunt posterior ends. (See Figs. 370, and 375, p. 1518.)

The larval stage lasts 7 to 10 days, and then the larva shrinks but remains surrounded by its old skin, termed puparium, which forms the covering for the barrel-shaped pupal stage. This lasts about 3 days when the adult fly emerges. This is termed a "coarctate" pupa. This fly is incapable of biting, the piercing organs being fused with the labium, but may transmit disease directly, carrying infectious material from the source, as faeces, to the food about to be ingested. Their rôle in typhoid fever is one of importance. By reason of its hairy sticky legs, habits of frequent defecation and constant regurgitation of the contents of the oesophagus, the housefly is an important agent in the spread of dysentery, cholera, infantile diarrhoeas and tropical ophthalmias as well as typhoid.

Auchmeromyia Luteola.—It is found throughout tropical Africa south of the Sahara Desert. Distribution coincides with that of the negro and the Bantu races. It does not occur in countries inhabited by Arabs and Berbers.

The larva of this African fly, the "Congo floor maggot," is a blood-sucker. The larva is about two thirds of an inch long and has a dirty-white, thick, leathery, wrinkled skin, otherwise resembling that of *M. domestica*. The adult fly resembles the blow fly but is yellowish brown. The fly deposits her eggs by preference in dry dust in cracks in the floor of the native huts. The larvae hatch in a few days, and seek blood within a few hours, crawling out at night to feed on the sleeping natives. They are said to survive for a month without food. This is the only known instance of a blood-sucking larva which attacks man. (Other species of blood-sucking larvae infest the nests of birds and the burrows of certain mammals.) Its attacks may be avoided at night by sleeping on cots a few inches above the floor.

Calliphora vomitoria (with a black bucca and reddish beard) and *C. erythrocephala* (with a brownish bucca and a black beard) are the common blow flies or blue bottle flies. They are large bloated flies, about one half inch long, with red eyes, and are bluish with a slight metallic lustre. The cheeks are hairy. They normally deposit ova on exposed food or decaying animal or vegetable matter of any kind, and on open wounds or ulcers of animals and occasionally of man.

Lucilia caesar, the common green bottle fly, is a smaller fly of shiny metallic green color with a bluish tinge. The cheeks are bare. Its habits are like those of *Calliphora*. If food contaminated with larvae of these flies is eaten, they may continue developing in the intestine and cause more or less marked disturbances (intestinal myiasis). In wounds or ulcers these flies prefer necrotic disintegrating tissue, but if this is not adequate they may invade and destroy living tissues. *L. sericata* (distinguished by its yellow palpi) is more actively parasitic, frequently attacking sheep on which it inflicts serious and even fatal injury. It may also attack man, and many cases have been observed in China. The larvae of both species (and also of *Phormia regina*, the wool maggot or black blow fly) have been used extensively in the treatment of osteomyelitis (Baer, 1931), although all are capable of injuring healthy tissue. Stewart (1934) has particularly shown that the species *Lucilia sericata*, which has widely been used as a surgical maggot, since it was supposed to be exclusively saprophagous, will attack and invade healthy living tissue.

Cordylobia anthropophaga (*Ochromyia anthropophaga*), the Tumbu fly or African Skin Maggot.—This is an African fly whose larvae develop under the skin of man and animals. It is known as the Ver du Cayor. The ova are deposited in dry sand, occasionally on clothing, not directly on the skin. After 3 or 4 days the larva emerges and by means of its mouth hooks, attaches itself (within 7 to 14 days) to the skin of the first animal with which it comes in contact, most often a rat or a puppy, or quite frequently a child. It then (painlessly) bores its way into the skin and produces a lesion like a boil which has a central opening through which the larva breathes. It resembles the Ver Macaque, is rather barrel-shaped and beset with small spines. At maturity (12 to 14 days) when it is about half an inch long it leaves the body and pupates in the soil. Repeated infections result in an immunity (largely local in the skin) which

prevents the development of the larva in the skin and is often associated with local anaphylactic phenomena.

Cochliomyia americana (*C. hominivorax*) (*Chrysomyia americana*) was shown by Cushing and Patton (1933) to be the imago of the parasitic "screw worm" in America. The adults resemble *Lucilia* but are somewhat larger and are distinguishable from them by the presence of black stripes on the thorax. The eggs, which number 250 or more, are deposited in or about the nose or ears or in open wounds of animals or man. The larvae have 12 segments and are encircled by narrow rings of minute spines which give them some resemblance to a screw. They burrow deeply into the tissues, causing extensive foul necrotic ulcerations, and may penetrate into the nasal sinuses. In 1935 it was estimated that there were over 100 human cases in the southern United States. In a series of cases compiled by Aubertin and Buxton the mortality was 8 per cent. The larvae mature after about 8 to 10 days, attaining a length of about 12 mm. They then leave the body and burrow into loose soil to pupate. *C. macellaria*, with which the preceding species has been confused, is primarily saprophagous, like *Calliphora*, and much less dangerous. It is distinguished chiefly by the character of the floor of the pharynx which is ridged longitudinally, whereas in the parasitic species this is smooth. The larvae of the latter have larger spiracles and larger thicker tracheal tubes. These flies are common in the warmer parts of both North and South America. A related species with similar parasitic habits, *Chrysomyia bezziana*, is common in Asia and Africa, and often causes human infection in India. (For treatment see p. 1514.)

Blood-sucking Muscid Flies.—*Stomoxys*, *Haematobia* and *Glossina* have a more or less elongated proboscis adapted for biting. *Stomoxys* has delicate palpi, shorter than the proboscis, and arista feathered only on the dorsal side with straight hairs. *Haematobia* has club-like palpi about as long as proboscis, and arista with hairs dorsally and ventrally. *Glossina* has thick-set but not clubbed palpi as long as the proboscis for which they serve as a sheath. The arista is feathered on the dorsal side with branching hairs.

Stomoxys calcitrans, the stable fly, has been described in Chapter III, African Trypanosomiasis. (Fig. 38.) *Stomoxys* may convey trypanosome (and other) infections mechanically, like the Tabanidae. This has been proved for *T. evansi* and experimentally for *T. brucei*, *T. gambiense*, *T. rhodesiense* and several others. The old view that it transmits poliomyelitis has been discredited.

Glossina, the Tsetse Flies.—This genus is limited to tropical Africa and includes about 20 species. Its description and importance has also been discussed in Chapter III.

Sarcophagidae

These "flesh flies" are distinguishable by the arista which is plumose to the midpoint and bare at the tip. They are usually thick-set, moderately large flies, dull colored with grey longitudinal stripes on the thorax. The abdomen is grey, checkered (in *Sarcophaga*) or spotted (in *Wohlfahrtia*) with black. They are viviparous. Most species deposit larvae on decaying flesh or vegetable material, but a few are parasitic in skin wounds or in the nasal or other cavities. Fatal cases have been reported. The larvae have powerful curved mouth hooks, a girdle of spines on each abdominal segment, and stigmal plates set in a deep cavity, each with three parallel vertical slits. The numerous species are difficult to identify.

Sarcophaga haemorrhoidalis is a widely distributed species which may give rise to intestinal myiasis. Cases have been reported in the United States. *S. carnaria* prefers to deposit larvae in the vagina when accessible.

Transmitted through Crustaceans.—Infections with *Dracunculus medinensis* and *Diphyllobothrium latum* through the medium of *Cyclops*, and paragonimiasis through certain species of crabs.

There are many arthropods which may accidentally bring about direct transference of disease, as with tabanid or stable flies which, following contamination of their biting parts with anthrax bacillus blood, might directly transfer the virus, when shortly afterward feeding on a man or animal, or in a similar way transfer the trypanosome of surra mechanically.

Many non-biting flies, in particular the house fly, and possibly cockroaches or other arthropods having access to our food or faeces, are important agents in the spread of typhoid, cholera, bacillary dysentery, and amoebic dysentery.

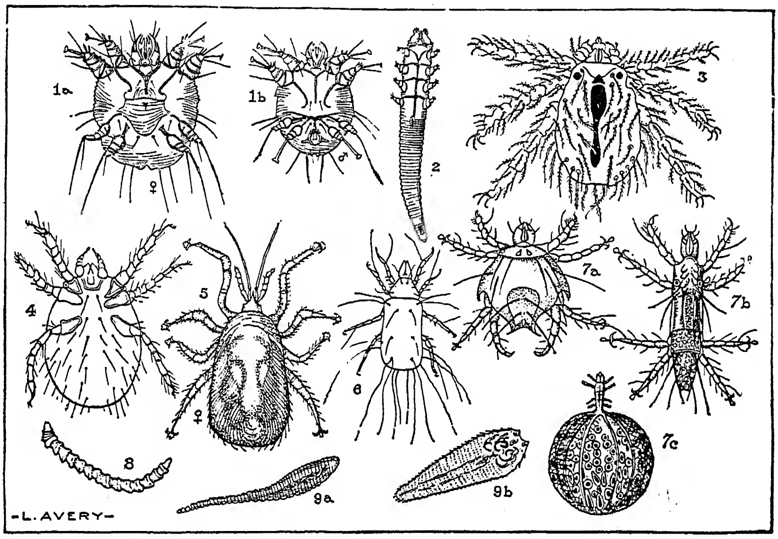

FIG. 359.—Arachnida exclusive of ticks. (1*a*) *Sarcoptes scabiei*, female; (1*b*) *S. scabiei*, male; (2) *Demodex folliculorum;* (3) *Trombicula akamushi*, hexapod larva (Kedani mite); (4) *Trombidium holosericeum* larva (*Leptus*); (5) *Dermanyssus gallinae;* (6) *Tyroglyphus longior;* (7*a*) *Pediculoides ventricosus*, male; (7*b*) *P. ventricosus*, young female; (7*c*) *P. ventricosus*, impregnated female; (8) *Armillifer armillatus;* (9*a*) *Linguatula serrata*, female; (9*b*) *L. serrata*, larva. Note: Figures not drawn to scale.

In addition to the importance of arthropods in the transmission of pathogenic organisms to man, arthropods themselves may play an important role in producing pathological conditions. Thus the larval stage of the myiasis-producing flies, the "chigger" (sandflea) and the sarcoptic mite may invade the tissues of man and cause important and disturbing lesions. Others, as ticks, may give rise to paralytic symptoms in some individuals by the injection probably of toxins or other secretions. Still others may introduce venoms, as certain species of spiders or scorpions or bees, giving rise to both local and general symptoms, sometimes followed by a condition of shock, with fatal results.

Bacterial infections of mosquito or other insect wounds, by scratching, are frequently reported. For a list of Arthropodan diseases see p. 1558 [Chap. LIII].

The Arachnida

The Arachnida differ from the Insecta in having the head and thorax fused together. They also have four pairs of ambulatory appendages, whereas the insects have three pairs. The Arachnida never have compound eyes—eyes when present being simple. Of the two orders of Arachnida of interest medically the Acarina is far more important than the Linguatulida.

Classification of the Arachnida

Order	Family	Genus	Species
Acarina	Trombidiidae	Trombicula	T. akamushi
			T. irritans
	Parasitidae	Dermanyssus	D. gallinae
		Liponyssus	L. bacoti
	Tyroglyphidae	Tyroglyphus	T. farinae
			T. longior
		Glyciphagus	G. domesticus
	Sarcoptidae	Sarcoptes	S. scabiei
	Demodicidae	Demodex	D. folliculorur
	Tarsonemidae	Pediculoides	P. ventricosus
	Argasidae	Argas	A. persicus
			A. miniatus
		Ornithodorus	O. savignyi
			O. moubata
	Ixodidae	Ixodes	I. ricinus
		Hyalomma	H. aegypticun
		Rhipicephalus	R. bursa
		Dermacentor	D. variabilis
			D. andersoni
		Boophilus	B. annulatus
		Amblyomma	A. hebraeum
		Haemaphysalis	H. leachi
Linguatulida	Linguatulidae	Linguatula	L. serrata
		Armillifer	A. armillatus

Acarina

Of the acarines the most important are the mites and the ticks. The acarines do not show any separation of the abdomen from the cephalothorax. A hexapod larva develops from the egg; this is succeeded by an octopod nymph which differs from the adult in not having sexual organs.

In addition to the four pairs of legs in the fully developed acarine there are two other paired appendages; the chelicerae, in front of the mouth, and the pedipalps on either side of the mouth.

Pathological Conditions Due to Arachnida

Trombidiidae (Harvest Mites)

These generally have a soft, more or less hairy integument and are often brightly colored. The two eyes are often pedunculated and the chelicerae are lancet-shaped and the palps project beyond the rostrum as claw-like appendages. A tip-like appendage on the apical segment of the palps is characteristic. A very common and annoying member of this family is the hexapod larva of the *Trombicula irritans*. It is in Europe designated *Leptus autumnalis*. Popularly it is termed "harvest mite," "red bug" or "chigger."

Redbugs or "Chiggers."—They are found in the fields in the autumn and attack both man and animals. They measure 150μ, and climb up the feet and legs, their small size enabling them to enter through ordinary clothing. They do not penetrate the skin but soften the skin with a secretion from the hypopharynx. Serum from the host, hardening, makes a closed tube through which the larval mite feeds. After becoming engorged (one or two days) they drop off and moult on the ground, to become 8 legged nymphs. The adult mites do not attack man. The condition (itching and redness) produced is at times called autumnal erythema. There is a *Trombidium* (Trombicula) in Mexico which has a predilection for the skin of the eyelids, prepuce, and navel.

Ewing (1938) divides the trombiculine larvae into 15 different genera. However in most instances the adult mites are as yet unknown. They have a wide distribution and species afflicting man are found in Australia, Japan and the East Indian Islands, southeast Asia, Europe, and North and South America. As yet, apparently they have not been reported from India or Burma or in Africa. In some of the East Indies, "red bugs" seem to constitute a more intolerable plague than anywhere else. The red bug dermatitis is probably due to a specific poison secreted by the mites. The inflammation of the skin may not be felt for 12 or even 24 hours after attachment of the mites. When the inflammation does commence there commonly appear large, red blotches on the affected parts which itch intensely and are made worse by scratching. After a day or so, the red blotches blister, and finally scab over. Sometimes the toxic effects are seen in the nervous system, occasioning irritability and insomnia and not infrequently fever. Newcomers to red bug infested regions may suffer severely the first season or two, but are said eventually to appear to build up a tolerance or perhaps an immunity. In such individuals, it has been reported that the occasional red bugs which do succeed in attaching themselves, although they may cause irritation, are said to be unable to engorge.

Morrow (1940) has prepared an antigen by grinding the chiggers and extracting with distilled water. Certain individuals gave a positive skin reaction to this antigen. Heat seemed to destroy a portion of the antigen, so that it became less irritating and induced less reaction. He believes that the extreme irritation produced by the bite of the chigger in some individuals is due to previous sensitization of man by some substance introduced into the skin and he thinks it probably possible to bring about a reduction of the irritation by desensitization with a suitable antigen.

Prevention and Treatment.—In countries where red bugs prevail it is advisable to sprinkle sulphur on the legs and inside the stockings, especially for those who have to walk through tall grass or brush where these pests abound. A hot bath shortly after infection, with soap and soda added to it, often gives much relief. For the itching weak ammonia or baking soda applied to the affected parts usually gives relief. Subsequently weak solutions of subacetate of lead or sulphate of copper are of benefit. Chandler, from personal experience, recommends mentholatum rubbed on the bites.

Trombicula akamushi is called the Kedani mite, and a typhus-like disease called tsutsugamushi which occurs in laborers harvesting hemp on the banks of certain Japanese rivers is transmitted by it. It is described in connection with this disease (p. 975). Other forms of *Rickettsiae* are transmitted by mites of the genus *Trombicula* such as *T. deliensis* in Sumatra and *T. hirsti* of Mossman fever in northern Australia.

Parasitidae (Chicken Mites, Red Mites of Poultry)

Of the Parasitidae, which generally have a hard, leathery body and styliform piercing chelicerae, delicate five-jointed pedipalps and styliform hypostome, only the *Dermanyssus gallinae* is of interest. This mite infests chicken-houses and sucks the blood of the inmates. In severe infestations, they may bleed the fowl to death. They will also attack man. Poultrymen may be troubled with a sort of eczema on the backs of the hands and forearms, similar to scabies, resulting from bites by these mites. They measure $350 \times 650\mu$. They have no eyes. The tropical rat mite, *Liponyssus bacoti* also will attack man and in some of the Southern states of the U. S. has been incriminated as a carrier of endemic typhus. The mite is said to transmit the rickettsial disease to its eggs. These mites may also produce a dermatitis.

Tyroglyphidae (Cheese Mites)

Grocers Itch.—Mites of this family live on cheese, flour, dried fruits, etc. They are small, without eyes, and have a smooth skin and a cone-like appearance of the mouth parts which are largely formed by the chelate chelicerae. They are chiefly of interest because of their being occasionally found in urine, faeces, etc., and being striking objects, the question of their pathogenicity arises. The *Tyroglyphus longior* has been associated with intestinal trouble (probably a coincidence, the patient having eaten cheese containing these mites). Other species of *Tyroglyphus* have been held responsible for "vanillism" in those who work with vanilla pods, or for "copra itch," in copra workers.

In many parts of the world, the dermatitis consisting of an itching urticaria is known as "grocer's" or "baker's itch." The mites of a species of *Glyciphagus* are frequently found in sugar and are the cause of this "grocer's itch." *Rhizoglyphus parasiticus* is reported to be the cause of an itch-like affection of the feet of coolies on tea plantations. Distinguishing points of these 3 mites are: The dorsum and legs of *Glyciphagus* are covered with plumose hairs; *Tyroglyphus* has both claws and suckers on tarsi, while *Rhizoglyphus* has only claws.

Other disturbances due to "jiggers," (sand fleas) are discussed, on p. 1502.

Sarcoptidae (Itch Mites)

Scabies.—The itch mites are small, eyeless and with a transversely striated cuticle Fig. 359. They live on the epidermis of man and various animals. The human itch mite, *Sarcoptes scabiei*, is an oval mite; the male is $250 \times 150\mu$, the female about $400 \times 300\mu$. Besides the difference in size, the male may be distinguished from the female by the fact that the third and fourth pairs of legs in the female have bristles whereas in the male the fourth pair has suckers (ambulacra). In these mites the rostrum is made up chiefly of chelate chelicerae with quite short three-jointed, rather adherent palpi. The female passes through four stages: (1) Larva; (2) nymph, resembles adult but has no sexual organs; (3) the pubescent female; (4) the egg-bearing female. A female becomes mature in about two weeks. The eggs, 140μ long, hatch out in four to five days. A pair of itch mites may produce 1,500,000 descendants in three months. The male does not burrow. Copulation takes place on the surface of the skin after which the male dies. Scabies is produced by the fertilized female who remains with her host, and not by the eggs, larvae, or pubescent female. The adult female burrows into the skin especially between the fingers, on the wrists and penis. In infants any part of the body may be affected. These tunnels are from 2 to 12 mm. long and tend to zigzag. They are dark gray, and at the entrance of the burrow the faeces accumulation makes a sort of minute dirty papule. A vesicular elevation marks the location of the mite at the blind end. Scratching obliterates these burrow lines. They are indistinct in those who bathe frequently (Gale des gens du monde). The tunnels have the egg-bearing female at the blind end; scattered all along are faeces, eggs and larvae, the eggs being next to the mother and the more mature young at the entrance to the gallery. The mites are more active when the patient's body is warm and relaxed, hence the nocturnal itching. A diagnosis can be made by demonstrating either eggs or larvae.

Ocular Myiases

The maggot of *Oestrus ovis*, a species of bot fly known as the sheep head maggot, sometimes invades the human eye. This species normally lays its eggs in the nostrils of sheep, in which place the maggots burrow into the frontal sinuses. In Algeria it lays its eggs at times while flying, without alighting, upon the eyes, nostrils and lids of shepherds. Infestation of the eye lids is also common in many parts of South America. In Palestine, reports have been made that the larvae frequently enter the eyeball. Another oestrid fly which attacks the eye of man is *Rhinoestrus purpureus*, a bot fly of the horse, so called on account of its purplish color. It is found in Central Europe and in Africa, as well as in Russia and Siberia. Portchinsky reports that Siberian peasants are not infrequently attacked by this fly, which rapidly darts toward the eye and deposits its young in that organ. The young maggots cause severe pain, so that the lids cannot be opened. Their removal is affected by dropping cocaine into the eye and then extracting them with pincers or by washing. Other "eye flies" have been discussed under *Oscinidae* p. 1509.

Urinary myiasis, of both urethra and bladder, has occasionally been reported. Usually the lesser house fly, *Fannia canicularis*, and the closely related latrine fly, *F. scalaris* have been encountered, the infection having probably occurred from eggs laid near the external opening of the urethra and the larvae working their way into the urethra and even entering the bladder. In one case reported by Patton of the larvae of *Psychoda*, he thought the larvae burrowed through from the rectum to the bladder. In one case reported by Chandler (1941) *Lucilia sericata* may have been the cause of the vesical disturbance.

Determination of Dipterous Larvae

There are certain points in the anatomy of dipterous larvae which must be considered in determination of the genus or family of the flies concerned in the various myiases. The broad extremity is the posterior one and the tapering one the anterior. The dark hook-like processes, which may be in pairs or fused, project from the anterior or head end and above them is a pair of projecting papillae. The second segment from the head has on either side projecting hand or fan-like structures with varying numbers of terminal divisions, 4 to 40 or more. These are the anterior spiracles.

The large terminal segment has on its posterior surface two chitinized plates with 3 slits of various architecture in each. These are the posterior stigmal plates and are the structures to which we pay particular attention in identification. In the early larval stages there is only one slit; in the second stage there are two. It is only in the fully developed larval stage that we note the characteristic 3-slit stigmal plates. The presence or absence of a rounded protuberance or button at the base of each stigmal plate should be looked for. The area carrying the stigmal plates may be sunken to form a pit.

Key to the Larvae Causing Myiases—Third Instar

(*Adapted from Banks after Fox*)

1. Body with spinous or fleshy processes laterally and dorsally or terminal........ 2
   Body without spinous or fleshy processes.. 3
2. Body flattened with long lateral and dorsal spinous processes................ *Fannia* (*Homalomyia*)
   Body with long tail-like process..*Eristalis*
   Body ending in two small fleshy processes bearing the stigmal plates; rather small species, body about 5 mm. long..............................*Drosophila*
   Same, body about 10 mm. long..*Piophila*
3. Body robust, ovate, cylindrical, rounded at ends, slightly depressed, or body pyriform..Oestridae 4
   Body truncate, broadly rounded at one end and tapering at the other (head) end.. 6
4. Larva flask shaped, heavily spined; posterior spiracle has three distinct slits...... *Dermatobia*
   Larva grub-like, heavily spined.. 5
5. Three sinuous spiracular openings..................................*Gasterophilus*
   Stigmal plate solid with many fine openings; button distinct, in depression in the plate...*Hypoderma*

6. But one great hook, posterior stigmal plates D-shaped with winding slits; no distinct lateral fusiform areas, tip of body with few if any conical processes. . *Musca domestica*
One hook; stigmal plates irregularly rounded, with winding slits. . . . . *Stomoxys*
With two great hooks; slits in the stigmal plates not sinuous. 7
7. No tubercles about anal area; no distinct processes around stigmal field. 8
Distinct tubercles above anal area; often process around stigmal field; lateral fusiform areas usually distinct. 9
8. Stigmal plates on black tubercles, lateral fusiform areas distinct. . . . . Ortalidae
Stigmal plates barely if at all elevated; lateral fusiform area indistinct, stigmal plates often continguous or nearly so; slits long and subparallel. . . . . Trypetidae
9. Slits in stigmal plates rather short and arranged radiately. 10
Slits slender and subparallel to each other. 11
10. Two tubercles above anal area; stigmal field with distinct fleshy tubercles around it. . . . . Anthomyiidae (except *Fannia*)
Four or more tubercles above anal area; slits of stigmal plates usually pointed at one end, bent, surrounded by dense chitinous ring. . . . . *Muscina*
11. Stigmal plates at bottom of a pit; no button; slits subparallel to those in opposite plate. . . . . Sarcophagidae
Stigmal plates not in a pit. 12
12. Chitin ring open mesio-ventrally; no button. . . . *Cochliomyia*, *Chrysomyia*, *Phormia*
Chitin ring closed. Button present. . . . . *Lucilia*, *Calliphora*

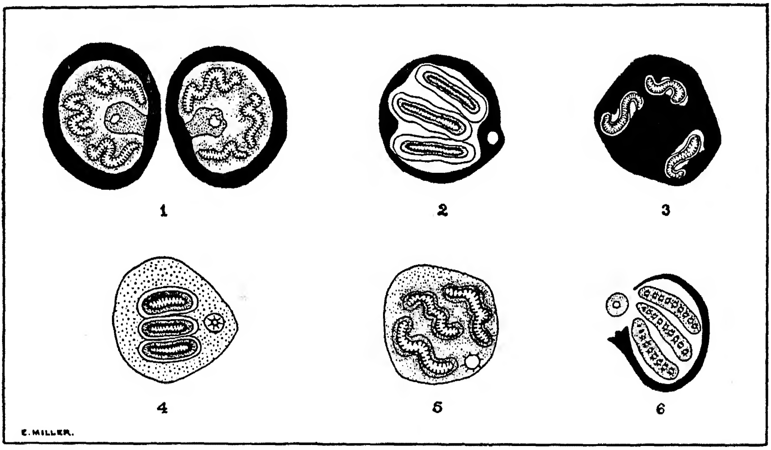

FIG. 375.—Markings of breathing slits on posterior stigmata of various dipterous larvae. 1. *Musca domestica*, showing both stigmata; 2. *Calliphora vomitoria;* 3. *Stomoxys calcitrans;* 4. *Auchmeromyia luteola;* 5. *Cordylobia anthropophaga;* 6. *Sarcophaga magnifica.*

Simuliidae (Buffalo Gnats, Black Flies).—These are small flies from 1 to 6 mm. long. The body is stout, and the thorax is humped. The wings are broad with conspicuous anterior veins. The legs are short, and the proboscis is short and inconspicuous. The antennae have eleven joints and are shorter than the head. Many species have been described. These flies are abundant throughout the world. The females (only) are vicious biters (by day light). They may occur in swarms so dense as to make infested districts almost uninhabitable and to cause serious destruction of live stock. The larvae, which are very characteristic (Figs. 311 and 376), require abundant oxygen. They are commonly found attached to slightly submerged rocks or vegetation in clear flowing streams; the American species noted below, occur in swiftly flowing mountain

In South Africa, Murray (1939) has found creeping eruptions of sandworm, as it is called, very common in Natal and Zululand. He has found that in these regions the burrows are produced by a mite, possibly related to *Tetranychus molestissimus*, which he reports is found in the Argentine and Uruguay, where it attacks both man and animals. The cracks in the skin are about 0.33 mm. in diameter. The mite, and sometimes its eggs, are usually easily demonstrable at the end of the burrow.

Another important cause of creeping eruption is the larval form of *Ancylostoma braziliense*, which is found in both cats and dogs of North

FIG. 377.—Larva migrans. (After Corson.)

and South America. Creeping eruption is apparently only caused by the third stage larvae of the above hookworm, positive results not obtaining from experiments with *A. caninum*, the common hookworm of dogs. Kirby-Smith holds that other ancylostome larvae may produce ground itch, but not creeping eruption. (See p. 1266 for a more detailed discussion of this form.)

Sandground (1939) describes a personal experience of 55 days of irritation, often infuriating, which followed the spilling on the finger of infected larvae of *A. braziliense* and of a *Strongyloides* species, both obtained from the faeces of the cat. There were intermissions, followed by the reappearance of symptoms. A piece of skin was cut. The epidermal tunnels were empty, but the larva was found coiled in the corium 1.5 mm. from the surface.

Treatment.—Bayley (1941) recommends for treatment of the form due to fly larvae that the skin be first thoroughly dried and cleaned with alcohol. Cedar wood oil is then used to clear the skin of the affected area, which is then examined with a ⅔ inch objective of a dissecting microscope, or with a good hand lens. The ends of the burrow must be carefully examined, as it is here that the fly larva may easily be found, where it

stands out clearly as a white, spherical mass. Having noted the position of the larvae, the skin is cleaned for operation and 2 minims of procaine, 1:1000, is used to desensitize an area half an inch in diameter, with the larva in the center, and cautery is then applied and a small burn produced. Each burrow must be examined, and whenever a larva is discovered the cautery should be applied. When many of the burrows are contaminated by bacteria, sulfanilamide has also been employed for its disinfecting effect. Usually in 3 days the small lesions are healed.

FIG. 378.—Creeping eruption, middle aged woman, showing multiple uninfected rapidly developing lesions of approximately two weeks' duration, both limbs being involved. (After Kirby-Smith, Dove and White.)

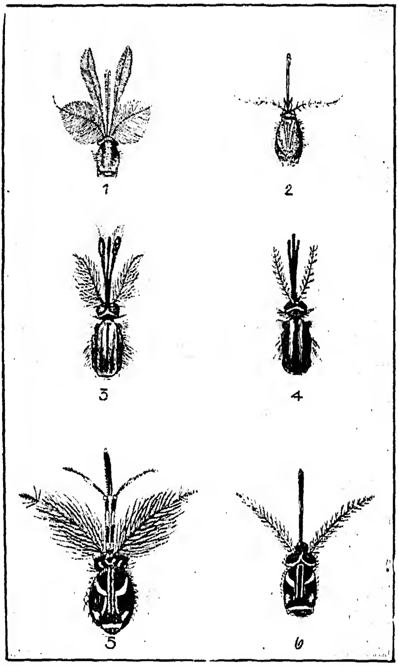

FIG. 379.—Heads etc. of mosquitoes: 1 and 2, male and female *Cutex quinquefasciatus;* 3 and 4, male and female *Anopheles;* 5 and 6, male and female *Aëdes aegypti.* (After Stitt.) (From P. H. Reports.)

For treatment of the form due to ancylostoma, Ketron has advocated the use of ethyl chloride applied as a spray to the extreme advancing point of the lesion until the tissue is frozen, about one minute's application usually sufficing. Frequently a second application is not required. Loewenthal (1939) also has found such treatment valuable and rarely proving ineffectual if, in addition, the advancing part of the line and the skin in front of it is treated with oil of chenopodium, either pure or in a dilution of 1:3 in castor oil. This is painted on daily until the larva ceases to progress. It is desirable to mark the extreme limit of the burrow by a superficial scratch so that one may know accurately whether or not the parasite is alive and progressing.

Mosquitoes

Mosquitoes (Culicidae) are of the greatest importance medically, not only from their influence upon health in general by reason of interference with sleep and possibly from direct transmission of disease, but, more specifically, they are the only means by which natural infections occur with such diseases as yellow fever, malaria, filariasis and dengue. In addition, a number of diseases of animals are transmitted by mosquitoes.

Dissection of the Mosquito.—In connection with the diagnosis of mosquito borne diseases and their prevention, dissection of the mosquito is often important.

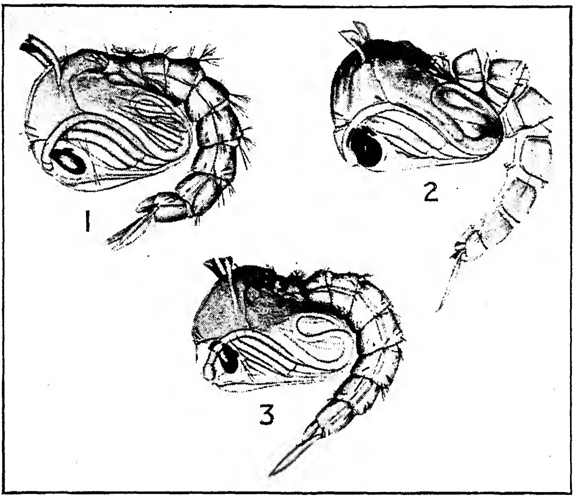

FIG. 380.—Mosquito pupae. (1) *Culex pipiens;* (2) *Aëdes aegypti;* (3) *Anopheles punctipennis.* (After Howard, Dyar, Knab, by courtesy of Carnegie Institution.)

The easiest way to secure a mosquito for dissection is to use an ordinary test tube. Slipping the open end of the test tube over the resting mosquito, by a slight movement, the insect will fly toward the bottom. Then quickly insert a cotton plug. If it is not desired to study the scales, the best way to kill the mosquito is by striking the tube sharply against the thigh; but if it is also desired to study the scale characteristics it is better to put a drop or so of chloroform on the lower part of the cotton plug. The vapor falls to the bottom of the tube and kills the mosquito. Take the mosquito out, pull off legs and wings, and then place the body in a drop of salt solution on a slide. It has been recommended to smear the surface of the slide with bile, wiping off the excess, before commencing the dissection in the salt solution. Then hold the anterior end of the thorax by pressure of a needle. With a second needle in the other hand, gently crush the chitinous connection between the sixth and seventh segments of the abdomen. Then holding the thorax in place, steadily and gently pull away the last segments. If this is done properly, a delicate gelatinous white mass will slowly float out in the salt solution. One should be able to secure the alimentary canal as far up as the proventriculus, which is just anterior to the stomach. The malarial zygotes develop in the stomach. Proceeding from before backward, we have the proventriculus, which is a sort of muscular ring at the opening of the stomach or mid-gut and marks the separation of the stomach from the oesophagus. Opening into the lower part of the oesophagus are the oesophageal diverticula or crops, which are food reservoirs. Occasionally in a dissection we pull out these structures which are three in number.

A. aegypti is a vicious feeder and very alert. Only the female bites, blood apparently being necessary for ovulation. It feeds especially during the morning and afternoon hours—much less commonly at night unless there is a light. To become infected with yellow fever virus it must take blood from a yellow fever patient in the first two or three days of the disease. After sucking the blood of a yellow fever patient the mosquitoes cannot transmit the disease by biting a person non-immune to yellow fever for a period of twelve days. After this time the mosquito remains infective for its life—in one instance fifty-seven days.

Aëdes albopictus (*Stegomyia scutellaris*) has a single silvery stripe down the center of the thorax. It breeds particularly in receptacles about the house. It is common in the orient. It has been proven to be a vector of dengue and (experimentally) of yellow fever.

Recent work has shown that several other species of *Aëdes* and related genera may convey yellow fever experimentally and perhaps under natural conditions.

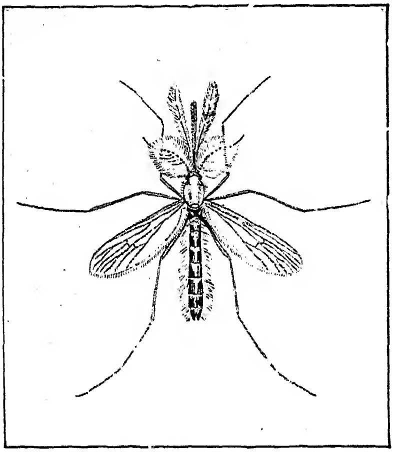

FIG. 382.—*Culex quinquefasciatus*, male. (After Howard.) (From P. H. Reports.)

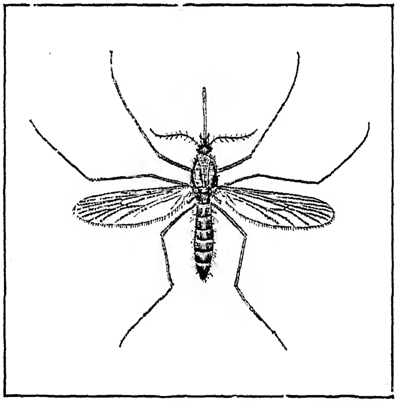

FIG. 383.—*Culex quinquefasciatus*, female. (After Howard.) (From P. H. Reports.)

Biraud (1935) and Faust (1940) have listed the mosquitoes other than *Aëdes aegypti* which have served as "efficient," or as "good incubators" of yellow fever virus, based on *experimental evidence*. (See table 1 opposite page.)

In jungle yellow fever (see Chapter XXIII), found in numerous areas in South America where *A. aegypti* is completely absent, the transmitting insect of the disease has not yet been demonstrated, although the infection has been transmitted from patients by *Aëdes aegypti* to rhesus monkeys.

A. leucocelaenus and **Haemagogus capricorni** and sabethine species have been found by Shannon, Whitman and Franco (1938) to be naturally infected in Brazilian forests.

In addition, the arthropods other than mosquitoes listed in table 2 (opposite page) have been reported to be efficient *mechanical transmitters only* (i.e., through interrupted blood meals). (Biraud, 1935.)

TABLE 1

MOSQUITOES OTHER THAN AËDES AEGYPTI INCRIMINATED IN YELLOW FEVER, BASED ON EXPERIMENTAL EVIDENCE

Species	Distribution	Breeding places
*Aëdes africanus**†.	Ethiopian.	Tree-holes, stumps; also semi-domestic.
*A. luteocephalus**.	W. Ethiopian.	Tree-holes, cut bamboo.
*A. simpsoni**†....	Ethiopian.	Tree-holes, leaf axils.
*A. stokesi**.......	W. Ethiopian.	Tree-holes, banana and bamboo stumps.
*A. vittatus**†.................	Ethiopian and Oriental.	Rock pools, cement drains, gutters.
A. irritans†..................	W. Ethiopian.	Crab-holes.
A. nigricephalus†..............	W. Ethiopian.	Crab-holes.
A. punctocostalis†.............	W. Ethiopian.	Crab-holes.
*A. fluviatilis**†................	Neotropical.	Rock pools along rivers.
*A. scapularis**†................	Neotropical.	Rain pools.
A. serratus†..................	Neotropical.	Rain pools.
A. leucocelaenus†..............	Neotropical.	Uncleared land.
*A. nubilus**†..................	Neotropical.	
*A. triseriatus**†...............	Nearctic.	Tree-holes.
*A. geniculatus**†...............	Palaearctic.	Tree-holes.
A. terrens†..................	Neotropical.	Tree-holes.
A. fulvithorax†...............	Neotropical	Tree-holes.
*A. albopictus**†................	Oriental and E. Nearctic.	Domestic, similar to *A. aegypti.*
A. variegatus (?) (syn. *A. scutellaris?*)†	Australasian.	Tree-holes, cocoanut shells, tins etc., in bush.
*Eretmopodites chrysogaster**†.....	Ethiopian.	Tree-holes, stumps; also semi-domestic.
*Culex fatigans**†.....	Tropical.	Domestic
C. nigripalpus........	Neotropical.	
*C. thalassius**†.......	W. Ethiopian.	Crab-holes.
*Mansonia africana**†.	Ethiopian, Oriental, Australasian.	Aquatic plants.
*M. uniformis**†..........	W. Ethiopian.	Coastal swamps and marshes.
M. fasciolata†...........	Neotropical.	Attached to sedges and *Equisetum.*
M. juxtamansonia†.......	Neotropical.	
M. chrysonotum†.........	Neotropical (Brazil only).	Attached to sedges and *Equisetum.*
M. albicosta†............	Neotropical (Brazil only).	Attached to sedges and *Equisetum.*
M. titillans†............	Neotropical.	Attached to floating water plants.
Psorophora cingulata†......	Neotropical.	In wooded areas and semi-domestic.
P. ferox†................	Neotropical.	Wild, in wooded areas.
Wyeomia bromeliarum†....	Neotropical.	Bamboo joints.
W. oblita†..............	Neotropical.	Water-holding plants.
Limatus durhami†........	Neotropical.	In natural and artificial containers.
Haemagogus janthinomys†.	Neotropical.	Forests.
H. uriartei†............	Neotropical.	Forests.
H. capricorni†...........	Neotropical.	Forests.

* *Efficient transmitters.* † *Good incubators.*

TABLE 2

OTHER ARTHROPODS REPORTED AS MECHANICAL TRANSMITTERS

Species	Distribution	Result
Stomoxys calcitrans............	Cosmopolitan.	Negative after 4–8 hours.
Ctenocephalides canis..........	Cosmopolitan.	Negative after 7 hours.
Cimex lectularius.............	Temperate zone.	Faeces ineffective.
Cimex hemipterus.............	Tropical.	Faeces ineffective.
Panstrongylus megistus*........	Neotropical.	Negative after 7 hours.
Ornithodorus moubata..........	Ethiopian.	Negative after 4–8 hours.
O. rostrata..................	Neotropical.	Negative after 4–8 hours.
Amblyomma cajennense........	Neotropical.	Negative after 3 hours.

* *Triatoma megistus.*

Aëdes variegatus (*Stegomyia pseudoscutellaris*) resembles *A. albopictus* but has white bands only at the sides of the abdominal segments. It is widely distributed in the Pacific Islands, in which it is the vector of filariasis (non-periodic strain of *W. bancrofti*). It bites by day.

A. togoi and **A. chemulpoensis** of Japan are effective filarial vectors, but in *A. aegypti* and *A. albopictus* development of the parasite is incomplete.

Psorophora.—Species of this genus have been incriminated as being passive carriers of larvae of a botfly (*Dermatobia hominis*). These larvae, when the mosquito alights on the skin of man, emerge from the egg case, penetrate the skin, and set up a cutaneous myiasis. See p. 1514. Species of *Aëdes* (*A. aegypti*, *A. albopictus*, *A. taeniorhynchus*, *A. sollicitans*, *A. vexans*, *A. cantator*, *A. dorsalis*, *A. nigromaculis*, and probably others) are biologically capable of transmitting the virus of equine encephalomyelitis. This is of particular importance in view of the increase in reported human cases of this disease. Human cases have been reported especially by Merrill and Ten Broeck (1935), Simmons, Reynolds and Cornell (1936) and Kelser (1938). The definite matter of transmission of the human disease has not yet been determined.

Uranotaenia.—A small genus, mainly of tropical distribution. The larvae live in ground pools and have a superficial resemblance to *Anopheles*, from the elongated black head and the habit of lying flat in the water, although the larvae are not surface feeders. The adults are ornamented with lines of metallic blue scales.

Megarhinus.—A genus of large showy insects of tropical and subtropical distribution. The adults do not bite, the proboscis being curved and adapted to extract honey from flowers. The larvae found in tree holes and similar locations feed entirely on other mosquito larvae. The species of this genus should be classed as strictly beneficial to man. On account of their restricted habitat the species are rare.

Mosquito Eradication.—Mosquito eradication in connection with malaria has been discussed in Chapter I. Being in practice a problem of engineering and municipal administration rather than of medicine, it will suffice here to indicate the means employed, according to circumstances, in ridding a district of mosquitoes.

In rural districts, where the malaria-carrying mosquito breeds, the measures especially applicable are: (1) Removal of collections of stagnant water suitable for breeding by surface or subsoil drainage, by permitting free access of the tide water, or by filling in as in the case of small ponds and wells; (2) introduction of fish which prey on larvae and pupae; (3) clearing away aquatic vegetation from the banks of streams and ponds, and (4) use of physical or chemical larvicides, as oil or Paris green.

In urban and suburban districts, where the mosquitoes transmitting yellow fever, dengue and filariasis are likely to breed, the measures are: (1) Piping the water supply to remove need of cisterns; (2) screening, covering and oiling all water containers, (3) removal of all rubbish that may hold water, as bottles and tin cans; (4) drainage of surface collections of water, or, where that is not possible, (5) employment of larvicidal measures; (6) as a substitute for these measures it has been shown that the introduction of the small mosquito-destroying fish into cisterns, tanks, etc., will prevent the breeding of mosquitoes Often fish cannot be depended upon to destroy all larvae in natural bodies of water where larvae and pupae are protected by surface vegetation.

A number of chemical agents may be employed as larvicides. The so-called Panama larvicide formulated and used successfully by Mason was compounded as follows: Add 200 pounds powdered resin to 150 gallons crude carbolic acid. Heat mixture to

212°F. until uniform liquid is obtained. Dissolve 30 pounds caustic soda in 6 gallons of water and add to mixture, stirring briskly. Keep at boiling point until a sample immediately emulsifies with water. This larvicide in a 1 to 1000 emulsion kills mosquito larvae in one to five minutes; in a 1 to 5000 emulsion in 30 minutes. It should not be used with oil or to dilute oil as the soapy characteristics interfere with satisfactory filming. Efficacy is impaired by exposure to air. Costs 25 to 30 cents per gallon. It is ordinarily sprayed or sprinkled in 10% emulsion to form not less than 1 to 5000 emulsion with the water treated.

Other larvacides are referred to in Chapter I. See also Appendix p. 1744.

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Chapter LI

POISONOUS SNAKES AND LIZARDS

SNAKES belong to the Class Reptilia and the order Squamata, suborder Ophidia. The two families to which poisonous snakes belong are the Colubridae (colubrine snakes) and Viperidae (viperine snakes).

Although the toxicity of the venom and the amount normally present are matters of great importance in estimating the lethal powers of species of poisonous snakes, the principal feature to be considered is the ability of the fangs to introduce venom into the tissues of the animal bitten. For example, in the Opisthoglypha there are fangs

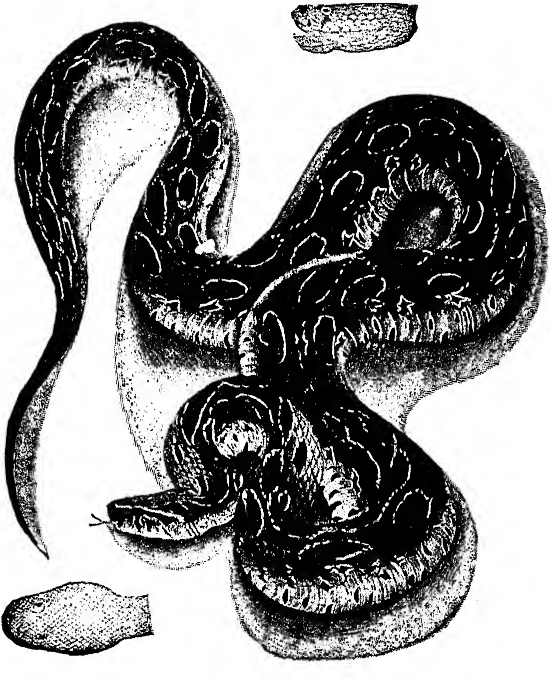

FIG. 384.—*Daboia russelli.* (After Mense.)

attached to the maxilla but these are placed posteriorly to the solid teeth in front, so that, since the venom cannot be inoculated, these snakes are from a practical point of view non-poisonous. Then, too, snakes in which the fangs are so situated have only a small poison gland and their venom is of low toxicity. In dangerous snakes the poison fangs are placed anteriorly, attached to the maxilla, which, in the poisonous Colubridae, is long and lies horizontal and, in the Viperidae, is short and lies vertical.

The non-venomous snakes are in the Aglypha series and have solid teeth. There has been a question as to a toxic saliva of some aglyphs but this is probably an allergic

manifestation. With the Protereoglypha, where belong the dangerous snakes, we have grooved or canalized poison fangs, attached anteriorly to the maxilla.

Colubridae.—The three series noted above belong to this very large family. The poisonous species belong either to the Hydrophinae (sea snakes), which have an eel-shaped tail and a rather flattened body, or to the Elapinae (land snakes), which have a round tail. As a rule, sea snakes live in salt water near the shore, but such snakes have been reported from a fresh water lake in the Philippines. They are of importance in the tropics and are a source of danger to fishermen. While their venom is extremely toxic, and their fangs situated anteriorly, the danger from them is minimized by their small heads and relatively inefficient bite. The Elapinae have short, strong fangs anteriorly located, and behind them small grooved (not canalized) teeth. The poison gland, which is the homologue of the parotid, has a duct located in the upper lip and terminating in a papilla. The poison duct does not enter the fang lumen but empties into muscular folds which surround the base of the fang, hence breaking off of a fang does not necessarily injure the duct. There is a succession of teeth in snakes, so that a new fang grows out if the original one is extracted.

Many of our harmless snakes such as the garter-snake and blacksnake belong to the Colubridae.

The cobras belong to the subfamily Elapinae and some are best known by a neck-like expansion or hood. The only poisonous colubrine snakes in the United States are the beadsnake (*Micrurus fulvius*) often called the Florida coral snake, and the Sonoran coral (*Micruroides euryxanthus*). Both of these snakes were formerly included in the genus *Elaps*.

The beadsnake is black with about 17 broad crimson bands bordered with yellow. Although small, they are very venomous. The upper jaw has anteriorly grooved fangs, which appendages are not present in the non-poisonous coral snakes, these latter having teeth in the upper jaw so that the wound shows 3 rows of punctures instead of 2 rows and one larger puncture on each side to mark the entrance of the fangs.

In Asia there are many important poisonous colubrine snakes, the cobra (*Naja tripudians*), the King cobra (*Naja bungarus*) and the kraits (*Bungarus fasciatus*).

All of the Australian poisonous snakes are colubrines.

Snakes of the United States (Stiles)

(*A*) Pupil of eye vertical; pit present; single row of ventral scales posterior to the vent; adults with head more or less triangular, constriction behind head more or less prominent.......................................Pit vipers (all poisonous).

(*B*) Pupil of eye circular; pit absent; double row of ventral scales posterior to the vent.

- (*a*) Color: first band on head black...................Coral snake (poisonous).
- (*b*) Color: first band on head not black............False corals (not poisonous).
- (*c*) Color: all others.......................................Not poisonous.

Viperidae.—The viperine snakes are generally characterized by a broad head, narrow neck, short and stumpy tail and a short upper jaw which, with the fangs, is directed obliquely backward. The rattlesnake (*Crotalus*), the copperhead (*Ancistrodon contortrix*), and the water moccasin (*A. piscivorus*) are widely distributed in the United States.

There are many harmless snakes which more or less resemble these "Pit Vipers," as the rattlers, moccasins and copperheads are called. This term refers to a deep hole or pit found on the side of the head between the nostril and the eye. It is a blind sac. The much dreaded "fer-de-lance" (*Bothrops lanceolata*) is a crotaline snake.

Some divide the Viperidae into the Crotalinae, which possess the pit, and the Viperinae which do not have this structure. Russell's viper (*Daboia russelli*) is one of the best known of the Viperinae and is one of the most important poisonous snakes of India.

The poison fangs are grooved or perforated and connected with the poison glands which resemble salivary glands and may be almost an inch in length in large snakes. The tongue is slender and forked and is a tactile organ.

The jaws are remarkable for their great extensibility, not only vertically, but laterally, permitted by the ligamentous connections of the two halves of the mandible or lower jaw.

As the fangs are directed backward it is necessary for the snake when striking to open the jaws widely and bend back the neck. The fangs are then brought forward and erected by the spheno-pterygoid muscles.* The snake bite is a combination of bite and blow. The functional fangs of colubrine snakes however are not mobile.

In addition to the possession of the pit, these vipers have a more or less triangular head and in particular a single row of large scales on the under surface posterior to the vent (anus), while the harmless snakes show an elongated oval head and two rows of large ventral scales posterior to the vent.

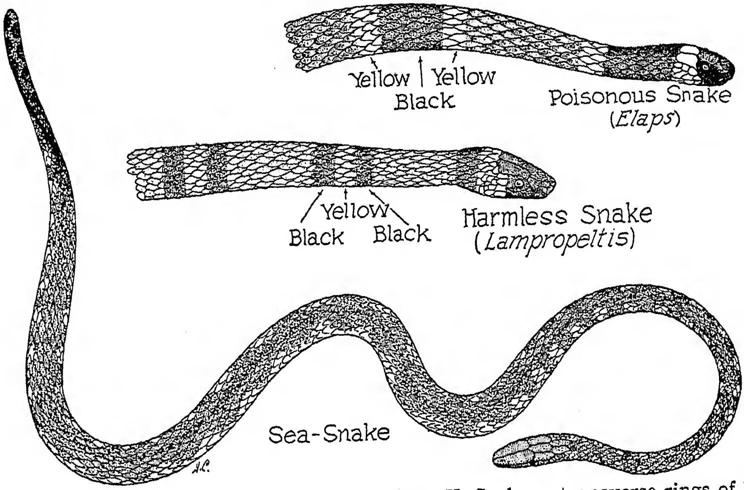

FIG. 385.—The poisonous coral snakes of the U. S., have transverse rings of black, vermillion and yellow. As differentiating these snakes from harmless ones which resemble them there are black rings bordered by two yellow ones, while with the harmless snakes a yellow ring is bordered by two black ones. The sea snake (*Enhydrina* species) has a rudder-like tail which is here shown twisted to one side.

Snake Venom.—In examining the wound made by a snake the two punctures of the fangs indicate the bite of a poisonous snake. If these fang-puncture points are far apart it shows that a large snake, and probably one capable of injecting a greater amount of venom, has given the bite.

When a snake strikes, the fangs move from the horizontal to the erect position, the mouth being widely open. When the fangs enter, the jaws close and pressure is exerted on the poison glands so that the venom pours out.

The idea that a snake exhausts its venom when striking is not true. Colubrine snakes may bite shortly after the first attack, and inject each time a lethal dose of venom. Fresh venom varies from an almost colorless fluid to one with a brownish or greenish color. It is viscid and quickly decomposes from the varied bacterial flora it contains. A number of years ago the injection of rattlesnake venom was used in the treatment of epilepsy but dangerous and even fatal reactions resulted from the pathogenic anaerobes at times present in the venom of snakes. Dried venom is quite stable in the dark, and retains its toxicity for years.

* Dr. M. E. Barnes points out that in vipers the venom gland lies between the fibers of the maxillary and the spheno-pterygoid muscles and the contration of the latter muscle in erecting the fang would also squeeze the venom gland and eject the venom.

The amount of venom varies with the size and condition of the snake, an adult cobra yielding about 1 cc. Acton and Knowles give the following table expressed in milligrams of desiccated venom.

Common cobra (mean yield)	317.0 mg.
Common krait (mean yield)	8.17 mg.
Banded krait (mean yield)	64.4 mg.
Russell's viper (mean yield)	108.0 mg.

They estimate the minimum lethal dose for man as 15 mg. with cobra venom and 42 mg. with the venom of Russell's viper (*Daboia*). The venom of the kraits is more potent, that of the very common Indian krait, *Bungarus candidus*, being given as 1 mg.

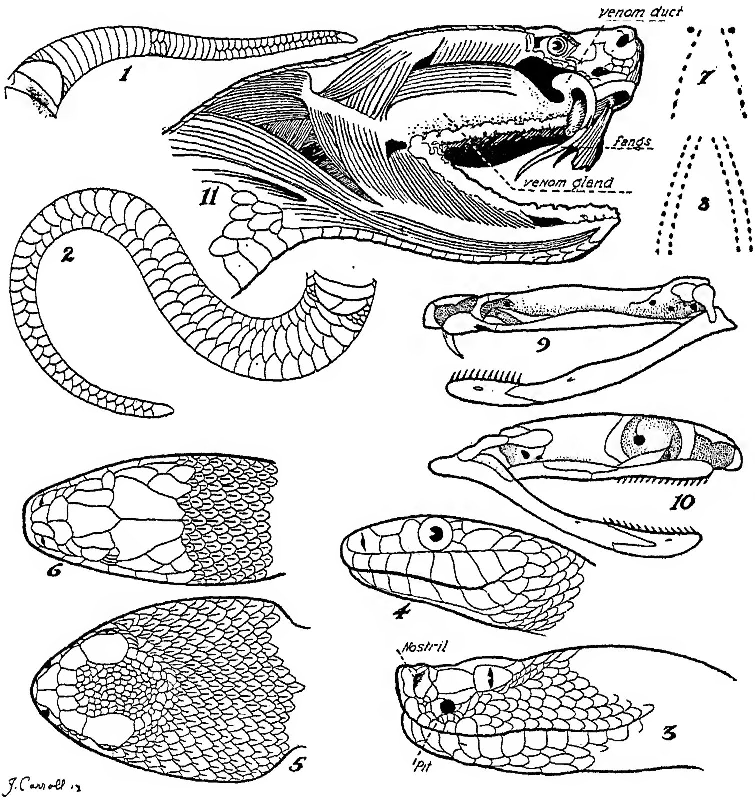

FIG. 386.—1, Single row of scales posterior to vent (poisonous snake—water moccasin); 2, double row of scales of harmless snake (*Natrix*); 3, side view of head of pit viper; 4, side view of head of harmless snake; 5, dorsal view of pit viper; 6, dorsal view of harmless snake; 7 and 9, bite puncture and skull of *Elaps;* 8 and 10, same of harmless snake; 11, poison apparatus of rattlesnake.

The cobra, after having bitten, remains attached for a short time while the *Daboia* strikes with the greatest rapidity and immediately releases itself.

Cobra and krait bites (colubrine snakes) produce more or less similar symptoms such as paralysis of articulation with nausea and vomiting and

later paralysis of the respiratory apparatus. There is only an insignificant reaction at the point of bite.

The venom is mainly neurotoxic, causing death by paralysis of cardiac and respiratory centers. Cobra venom is also very haemolytic. This haemolysin is activated by the normal complement of the serum of the animal poisoned, the haemolysin as contained in the venom not being toxic when alone. Lecithin also has the property of activating the haemolytic substance in venom.

In rattlesnake bites (viperine snakes) there is marked pain at the site of the wound with much swelling and haemorrhagic infiltration. The

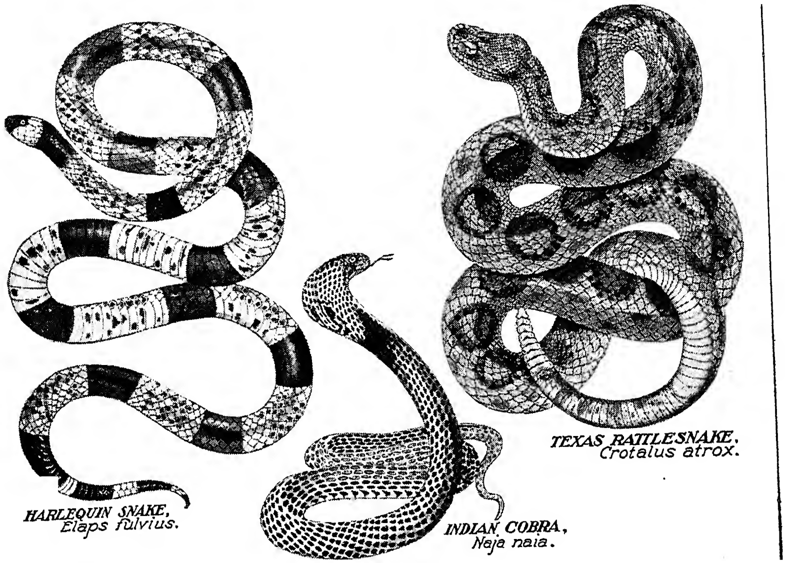

FIG. 387.—Important poisonous snakes.

swelling and petechial mottling spread up the limb from the point of entrance of the venom. Cold sweats, nausea, cardiac depression, and syncope are common. An exception to this general rule is *Crotalus terrificus*, whose venom is strongly neurotoxic, affecting vision and respiratory centres. The local effects are slight.

Rattlesnake venom is active chiefly on account of its haemorrhagin, or rather endotheliolysin, which destroys the endothelial lining of blood vessels.

The haemolytic (haemotoxic) effects of the venom of the West Indian and Central American vipers are most marked—haemorrhages from the conjunctivae and stomach occurring along with reflex vomiting. There is marked damage to the blood vessel walls, death occurring in coma in about eight hours in the absence of antivenin. Even with such treatment transfusion may be necessary. Of the American pit vipers, the rattlesnake venom is the most toxic and that of the water moccasin least so, but the necrotizing power of the latter is more marked.

Venoms may also contain proteolytic ferments which may account for the softening of muscles in snake-bite cases. The toxic effect of the venom takes place without an appreciable incubation period, hence different from true toxins.

The most venomous snakes seem to be the sea-snakes (*Enhydrina*). This venom is almost entirely neurotoxic.

The tiger snake of Australia is almost equally venomous and the krait (*B. candidus*) next. The rattlesnake is about one-fifth as venomous as the krait. Clark (1942) in the identification of over 3,000 snakes, especially from Honduras and Panama finds the commonest poisonous snakes to be the *fer de lance Bothrops atrox; B. lansbergii* and *B. nasutus* (*hog-nosed vipers*), *B. schlegelii* (horned palm viper), *B. lateralis* and *B. nigroviridis nigroviridis* (both tree snakes), *B. godmani*, *B. nummifera* (jumping snakes), *Lachesis muta* (bushmaster). It is noted that *Crotalus terrificus* is found in Panama, Costa Rica and Colombia. Six species of the coral snakes were found particularly in Panama of which *Micrurus negrocinctus negrocinctus* was the most common.

Certain venoms greatly increase the coagulability of the blood so that intravascular thromboses may occur. It is chiefly with the venoms of *Daboia* and *Bungarus* that such thromboses are likely to occur and this accounts for the almost instantaneous death which at times results from bites of such snakes, when the toxin is injected directly into a vein.

Treatment.—The non-specific treatment of snake-bite poisoning which has usually been recommended is: (1) Apply a tight ligature above the site of the bite for 20–30 minutes. The ligature, which should preferably be a rubber band, is to be applied about a single-bone extremity, not about one with two supporting bones. (2) carrying a piece of rubber gauze is recommended, which is cut and placed on the site of the bite. Suction by mouth should then be kept up steadily for at least one-half hour, if no antivenin is available. If antivenin is at hand, it should be administered at a distance from the site of the bite and the suction continued. Incision increases the chance for the invasion of secondary infection.

Bannermann has shown that a dog bitten by a cobra cannot be saved by free incision and the rubbing in of permanganate crystals. It may, however, be saved by the immediate injection of 10 cc. of a 5 per cent solution of permanganate, but not if two minutes has elapsed. Bites from the *Daboia* are fatal, however the permanganate be applied. He, therefore, does not consider the permanganate treatment of any practical value. Rogers thinks that Bannermann's experiments with dogs do not give a true idea of the value of permanganate because he has had success in experimenting with cats and because he believes it has saved human lives. Chromic acid injections (1 per cent) have been recommended. Acton and Knowles consider potassium permanganate as unreliable and recommend subcutaneous injections of a 5 per cent solution of gold chloride. These local injections are efficacious if used before the venom has been absorbed but they have no effect on venom taken up by the circulation. Intravenous injection of permanganate is not only without effect but is dangerous. Amaral states that the ligature will not prevent the venom from spreading and may accentuate the proteolytic and cytolytic action. In his opinion permanganate solutions in active concentrations have a deleterious action on tissues. Recent authorities counter indicate the use of potassium manganate.

Internally alcohol does not seem to be of any value; in fact, many of the deaths have been attributed to excessive ingestion of whiskey. Strychnine in large, almost poisonous, doses was highly recommended in Australia, but the statistics seem to make the value of this remedy doubtful.

In an article on snake bite, N. Hamilton Fairley (1934) states that early free excision combined with mechanical suction is the only method of local treatment likely to be successful in body bites. Immediate application of a ligature and free excision (3 by 3 cm.), down to the muscles, was the only effective local treatment in sheep bitten by tiger snakes. He refers to the work of Crimmins (1927), advocating ligature and incision combined with suction by a breast pump, and that of Jackson and Githens (1931), in which incision of the wound bite, combined with suction by a Bier's apparatus and irrigation with saline, is recommended. Fairley regards these methods as useful accessories to ligature, incision and excision. As regards the use of permanganate, Raymond Ditmars (Cecil's Medicine) states "Nothing could be more foreign to the treatment of snake bite than such practice." For local treatment he advocates deep incision and forced suction. *Cauterization should never be used.*

Allen (1939), particularly on account of the evidences of local diffusion and local binding of the venom, also does not recommend incisions. He has discussed in detail all the local measures in the treatment of snake bite. He believes the use of an *occlusive* tourniquet is harmful. The reason for this is because the poison is too slowly absorbed and destroyed and the circulatory stasis increases the local necrosis and the consequent absorption of toxic tissue products. However, he thinks that the earliest possible excision of a large area of tissue may be beneficial. In still more deperate cases, he points out that amputation is a more positive remedy. He also thinks that the tourniquet may be serviceable, with or without refrigeration, as preliminary to delayed amputation.

Herbert Clark (1942) who has had more than 30 years experience in Central America in the study of venomous snakes and the treatment of snake bite, emphasizes that in treatment the essential measures to be effective should be taken immediately after the bite. The first step should be to kill the snake for identification. A tourniquet, sufficiently tight to stop venous but not arterial flow, is advocated. It should be released for a few seconds every 10 minutes. Extraction of the venom by suction should be started at once. Suction may be applied by the mouth over a thin sheet of rubber laid over the bite. This should be continued vigorously for five minutes and the site should then be washed, antivenene given and suction repeated. Incisions at the site of the bite are not advised as the channels made by the fangs are raw and additional incisions increase the raw surfaces and therefore hasten absorption. Antivenene should be given subcutaneously and the tourniquet should be kept in position for an hour after the administration of antivenene. Alcohol is contraindicated, and permanganate cannot reach the droplets of venom beneath the skin.

In Central America antibothropic serum can be used with a good chance of effectiveness in all cases, though 80 to 85 per cent of the bites are due to species of Bothrops.

Duran-Reynals (1939) has pointed out the spreading factor in certain snake venoms in relation to their mode of action.

Antivenins.—The active agents of snake venoms may be either of the nature of haemorrhagins, neurotoxins, or fibrin ferments. In colubrine snakes the neurotoxin vastly predominates whereas with the viperines it is the haemorrhagin. Certain Australian snakes contain all three bodies in about equal proportion, whereas with the rattlesnakes of America it is almost entirely the haemorrhagin which causes the poisoning. The Micrurus (Elaps) of Florida is a colubrine snake and its venom is neurotoxic in nature.

The cause of death in colubrine snake bites is chiefly from paralysis of the respiratory centers whereas with the pit vipers it is chiefly from haemorrhages in the vital organs. Antitoxins have been prepared against both viperine and colubrine venoms and these are specific; thus a colubrine antivenin will not be of value against a viperine bite. Antivenins should be administered either intravenously or intramuscularly. The amounts recommended for injection to neutralize a fatal dose of snake poison vary from 100 to 300 cc. of the antivenin serum. There is no accurate method of standardization.

When Calmette (1894) first produced antivenin the idea prevailed that it was useful for any snake venom, a view soon found to be untenable. There are now institutes in many parts of the world where antivenins are made to combat the local venoms; thus in the U. S., we have the Antivenine Institute of America which produces an antivenin for rattlesnake, copperhead and water moccasin venom. These venoms are chiefly haemorrhagic. Previously, the toxicity of some venoms made the immunization of horses precarious, but methods of detoxication are now being used which are more successful. Both monovalent and polyvalent sera are produced. Often, when it is impossible to determine the species of the offending snake, a polyvalent serum is indicated. Antivenins are given either intramuscularly or intravenously. With highly poisonous

venoms intravenous therapy is indicated. Fairley emphasizes that dosage is in inverse proportion to body weight, so that children may require several times the amount of serum sufficient for a heavier adult. This is connected with the natural neutralizing power of the blood stream. A large individual, having more blood to partially neutralize venom than a smaller person or a child, requires less antivenin. Owing to varying strengths of antivenins (concentration methods) one should depend for dosage on the instructions accompanying the product. Besides the local and specific treatment for snake bite one should put the patient at rest physically and mentally, as psychical shock is an important matter with some snake bite patients. Fairley also recommends black coffee or caffein. Avoid strychnine and alcohol, and in particular morphine.

Lizards

Lizards are non-poisonous, with the exception of the two Gila monsters (*Heloderma suspectum* and *H. horridum*). The first is found in Arizona and New Mexico (Gila river valley), and the second named in south western Mexico. They are about 2 feet long, heavily built, and covered with small tubercles. The name monster is most applicable. The poison fangs are in the lower jaw, and the bite of these apparently sluggish creatures may cause death. The symptoms of poisoning often start with paralysis. Dyspnoea and convulsions may follow. When aroused, they are very vicious and it is as difficult to open the closed jaws as in the case of a bulldog. They lay parchment-like eggs in the sand of the desert.

(For references see end of Chapter LII. P. 1550.)

Chapter LII

POISONOUS ARTHROPODS, FISH AND COELENTERATES

Venomous Arthropods

Spiders.—Spiders belong to the class Arachnida, order Araneida. There are numerous families, divided into various genera. As a rule spiders secrete a venom which is capable of poisoning the small animals used as food, but it is only in rare instances that the venom is poisonous for man. Individual idiosyncrasies may make one person susceptible to spider or other arthropod bites whereas others do not suffer.

Reports of illness following spider bites are very rare and many of these are due to secondary infections with pyogenic bacteria.

The dread of spiders is probably connected with attributing the hysteria of the Middle Ages, or tarantism, to the bite of *Lycosa tarantula.* As a matter of fact the bite of this spider produces only a localized erythema without general symptoms.

Experiments have shown that most of the common spiders not only are unwilling to bite but, even when almost forced to do so, are unable to penetrate other than the most delicate human skin. Even then the bite has only the effect of a pin prick.

In America we apply the term tarantula to a large, dark, hairy ferocious-looking spider of the family of Aviculariidae. None of these are dangerous, in spite of folklore to the contrary. (Barbour 1941.)

However certain species of the genus *Latrodectus* produce systemic symptoms rather than local ones. A few are very poisonous:

In southern Europe, *L. tredecimguttatus* ("the malmignatte"; in New Zealand, Australia and the Philippines, *L. hasselti* (known as the "katipo"); and in North and South America, *L. mactans*, *L. curacaviensis* and *L. geometricus* are common. In Turkestan, *L. tredecim guttatus* (the "Karakurt spider"); in Australia, *Atrax robustus* (the "funnelweb spider"); and in South Africa, *Latrodectus indistinctus* (the "Kroppie spider") are much feared.

The venom of the Kroppie spider has recently been studied by Shapiro and by Finlayson (1939) and its bite is not at all uncommon in South Africa. The toxin of the poison glands has been shown to be a powerful haemolysin. It has a marked depressant effect on the cardiac muscle. Rigidity and spasm of most of the muscles supervene, especially those of the abdomen, which become boardlike, and the condition may simulate appendicitis. Sloughing of the skin in the neighborhood of the bite may occur. Finlayson has found that the haemolytic properties of arachnolysin (that is, a solution of the dried body of the insect) differs somewhat from that of the pure venom. The former readily haemolyses human corpuscles as well as those of the rabbit.

For *treatment*, intravenous injections of calcium gluconate 10 cc. of a 10 per cent solution has been recommended for the relief of pain and for decreasing the muscular spasm. Finlayson has prepared a serum which neutralizes the venom which he recommends for treatment.

The bite of the species *L. kapito*, of New Zealand, is said to cause slowing of the pulse and respirations and produce tetanoid manifestations.

Latrodectus Mactans.—In the United States, this species, often called the "black widow" or "hourglass" spider, has been held responsible for symptoms of poisoning in about 400 cases, with a record of 16 deaths.

These spiders have been reported from many states, particularly Western and Southern ones, with about half of the cases from California. This species, however, has also

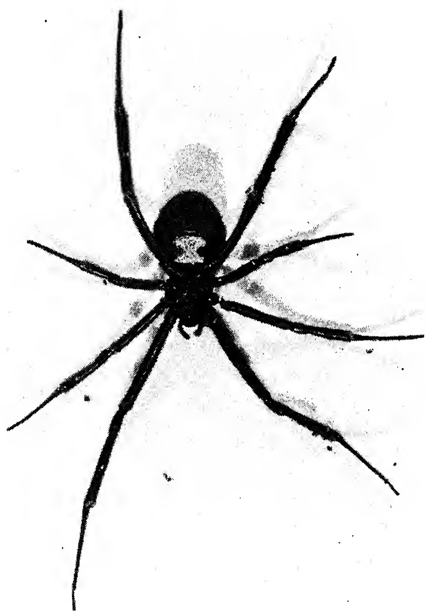

FIG. 388.—*Latrodectus mactans*, female. (Black widow.) Ventral surface showing orange-red hour-glass spot. (Original.) Approximately actual size.

been found in southern Canada, Cuba and Mexico and as far south as Peru and Chile. In his book on entomology, Herms gives an excellent description of it. The female is about an inch in length—the male is much smaller. The globose abdomen of the female stands out like a beautiful highly polished black pearl. She is exceedingly active and most aggressive. An interesting fact is her killing the male after he has served the ends of species preservation.

It has been stated that the more husbands she has disposed of the greater the virulence of her venom. This spider is usually found in old out-buildings, chiefly under privy seats, or dry cracks in brick or concrete work supporting such buildings. They also can be found in new houses and occupied ones, even in occupied beds. The web is rather coarse and does not show the regular symmetry of many spider webs. The egg cocoon is attached to the web, and any attempt to dislodge it is resented by the alert mother. There are more than 100 rather large eggs in the cocoon, which is spun during

the summer. The small grey spiderlings, which hatch out in about a month, are very active. After several molts, at each of which there is increasingly darker color, there develops after a number of months (and generally in the spring), a mature female with the deep orange spots on the ventral abdomen which enable one to identify this species. The spots vary from a striking resemblance to an hourglass, with the spots apposed at their apices, to an arrangement like a Maltese cross with 4 spots at right angles. Again there may be only one spot. Cases of bites generally occur in the summer and autumn.

W. H. Chapman (1936) notes the severe systemic symptoms of four cases observed by him—rather insignificant pain at the site of the bite (which may not be manifest), to be followed in about 30 minutes by marked pain in various parts of the body, particularly of the abdomen, when the rigid muscles make one suspect "acute abdomen."

Hargreaves and MacKenzie (1942) have reported a case with such symptoms due to the bites of *L. lugubris.*

The pain is excruciating and scarcely responds to morphine. The pulse is slow and the respiration embarrassed. The temperature may be raised and the leucocytes increased. There may be a macular rash. Spasm of the back and thigh muscles may be noted. The venom is apparently a toxalbumin and its most damaging action is on the nerve endings, as in cobra poisoning.

For treatment, hot packs may be of value. The administration of alcohol has been condemned. Gilbert and Stewart (1935) recommend intramuscular or even intravenous injections of calcium gluconate (10 cc. of a 10 per cent solution).

Injections of specific antivenin have also been employed. One such immune horse serum is prepared by Mulford and Company. However, it is recommended that the patient should first be tested for serum sickness and, if necessary, desensitized before the intramuscular injection of the antivenin. Smith and D'Amour (1939) have found that a most effective antiserum against the venom of the black widow spider has been produced in sheep. However, it is necessary to use a large number of spiders, about 3000 per sheep, over a 6 months period. This preparation has been made commercially available by Squibb.

MacKinnon (1938) has found that this same species (*L. mactans*) is found in Uruguay, where it gives rise to similar symptoms to those discussed above. He reports 4 cases, in one of which a boy of 11 years was bitten in the subclavicular region. Death occurred in 36 hours. Another species of spider, *Glyptocranium gasteracanthoides*, found in Peru, gives rise by its bite to gangrenous lesions, haematuria, and additional symptoms as in *Latrodectus* poisoning. Its bite also may be fatal.*

Scorpions.—These arachnids belong to the order Scorpionida. The scorpions of temperate climates are usually small but those of the tropics may attain very large size, even 7 inches in length. The last abdominal segment terminates in a ventrally curved spine. This segment carries the poison glands.

Scorpions have formidable claws or pedipalps, with which they seize their prey and then by a downward movement of the tail-like abdomen they pierce the prey with the spine and thus introduce their venom. The poison of some of the large scorpions, as *Buthus quinquestriatus*, seems to resemble in action that of the cobra venom. Although the larger scorpions are particularly to be dreaded, especially where young children have been bitten (mortality of bites of *B. quinquestriatus* in young children practically 50%) the effects of the bites of the small scorpions found in the Southern U. S. and California are probably never fatal although they may be quite painful and produce slight general symptoms.

* Sampayo (1944) reports many hundreds of cases in Buenos Aires Province, Argentine, frequently in rural laborers who with exposed chest handle hay or load cereal bags. He has isolated the venom which contains a neurotoxic substance which has a diffuse excitatory action throughout the entire central nervous system.

B. quinquestriatus, in the Egyptian Sudan, also gives rise to a high mortality reaching 60 per cent in children under 5 years of age. Waterman (1938) reports that in Trinidad the mortality in children under 5 years of age is 25 per cent, although the majority of individuals stung by this scorpion in Trinidad are over 13 years of age. In central northern Mexico, the death rate from scorpion sting, principally of the species *Centruroides suffusus* (the durango) has averaged 100 per 100,000 *per annum* for several years (Faust 1940); the majority of the victims are from 1 to 7 years of age. Aged persons, however, are very susceptible, and young adults have been known to die within an hour after being stung.

Species of *Buthus* are also found in southern Europe, as well as in northern Africa. Also, the poisonous black scorpion, *Euscorpius italicus* is found in these localities. *Scorpio maurus* is also a poisonous species in Egypt and Tunis, while in India species of *Tamulus* and in Trinidad the black *Tityus trinitalis* and in Brazil *T. servulatus* are especially dangerous. The species *Centruroides suffusus* occurs not only in northern Mexico but from the southern part of the United States to Panama. The species *Buthus martensi* has been found poisonous in Manchuria.

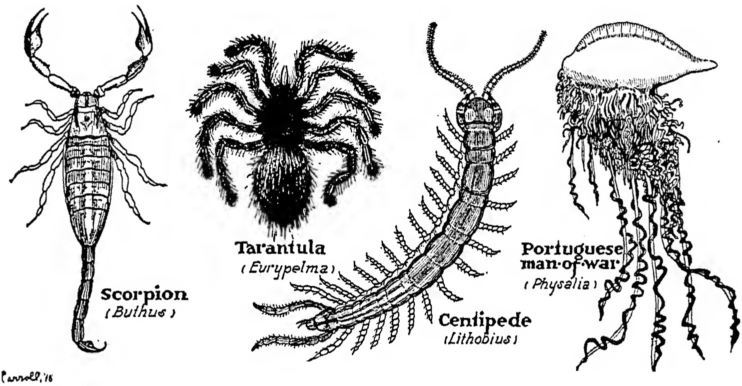

FIG. 389.—Poisonous arthropods and coelenterates.

The importance of scorpion poisoning has been emphasized recently by Sergent (1938) in North Africa, Basu (1939) in India, Faust (1940) in northern Mexico and Shulov (1942) in Palestine. The studies of Waterman (1938) emphasize the importance of poisoning by scorpions in Trinidad, where, however, only the severe cases came under medical observation. The majority occur in the cane fields of the cocoa plantations, though the scorpions often lurk in the shoes and clothing.

In 5 years, at one hospital in the cane growing district, 689 cases were admitted: In the last year 189, and 33 deaths, or 4.7 per cent. The fatality rate is greatest in the very young. Of 16 under one year, 6 died; but up to the age of 5 years, in 88 cases there were 22 deaths. Twenty-five per cent of the cases occurred under 5. Between 6–10 years there were 96 cases and 5 deaths, 5.2 per cent. In the second decade there were 5 fatalities among 190 cases, or 2.6 per cent. Of 324 over 21 years, only one died. Death might take place at any interval, from 1½ to 42 hours.

The symptoms are burning pains, usually lessening in 15 minutes. The patient feels sick and presents salivation, nausea and vomiting, with profuse sweating. The vomit may be dark coffee-ground in color. Respirations may be as rapid as the pulse, but though there is dyspnoea there is never cyanosis. Reflexes are increased. In infants and children,

convulsions are common and in such cases the prognosis is bad. Excretion may occur in poisonous amounts in the milk and Waterman observed a case in a woman stung shortly before nursing her child.

The latter showed symptoms of scorpion poisoning and died. A similar condition had been recorded after snake bite. At autopsy, all the viscera were congested, the lungs oedematous, due probably to cardiac failure, small subserous and submucous haemorrhages occurred. The pancreas may show haemorrhages.

Treatment formerly consisted of potassium permanganate administered intravenously, but this has been given up. However, some still recommend 2 cc. of 0.25 per cent colloidal manganese intramuscularly, repeated if necessary. Waterman suggests the administration of glucose 10 per cent rectally, or 3 per cent subcutaneously, followed by insulin. The treatment otherwise should be symptomatic.

Antivenin treatment has been particularly recommended by a number of investigators. An antivenin made with goats is available for the Brazilian form and is obtainable from the Serum Institute at Butantan. Shulov and Sergent have also particularly recommended serum treatment in Asia and Africa.

Sergent has found the most dangerous species in North Africa to be *Prionurus australis*. He reports antivenin treatment in 33 patients (19 children, one old man, and 13 adults) seriously ill and thought to be dying. Of these, 26 recovered and 7 died; 6 children and one adult. In the case of 8 others (7 children and one old man), in all of whom a fatal issue might be expected, all recovered. Thus in 41 cases, 34 ended in recovery; 82.9 per cent. In 66 cases with mild symptoms, all recovered.

Myriapods.—These arthropods are divided into the orders, Diplopoda, or millipedes, and Chilopoda, or centipedes. Millipedes have a more cylindrical body than centipedes and, with the exception of the appendages coming from the most anterior somites, have 2 pairs of legs to each segment, whereas the centipedes have only one pair to each segment.

Millipedes have no fangs and it is generally accepted that they are harmless. However, several species are of some medical interest, as species of *Julus* and *Fontaria virginiensis* may serve as intermediate hosts for *Hymenolepis diminuta*.

Centipedes have poison glands at the base of the first pair of legs. The legs terminate in a powerful claw, at the tip of which is the opening for the expulsion of the venom. The small centipedes which are found in temperate climates rarely give rise to more than local symptoms, but the large tropical ones, as for instance *Scolopendra gigantea*, which may be 10–12 inches long, have been reported in some instances to cause death in children by their sting. They give rise to necrotic local lesions at the sites of the two punctures, and, in addition, may produce general symptoms of vomiting, headache, fever and even coma. For treatment, local application of solutions of ammonia 1:5 or 1:10 are recommended. Hypodermic injections of morphia may be necessary to allay the pain.

Bees, Wasps and Ants.—These arthropods belong to the order Hymenoptera of the class Insecta. The venom of bees is ejected through the sting, which is at the end of the abdomen. In addition to the formic acid, there is also a neurotoxin in the venom. Experimental immunological tests suggest that bee poison is related to viper and rattlesnake venom (Phisalix). When a bee stings, the stinging parts are usually left in the wound, to continue by muscular action to force out the contained venom into the tissues of the victim.

As a rule, the effects of a bee sting are entirely local, but cases have been reported of general symptoms ensuing, such as fever, dizziness, dyspnoea and urticarial lesions. The symptoms generally disappear within a few hours. However, the introduction of the venom into the conjunctiva is apt to give rise to more serious results, the tissues quickly becoming greatly inflamed and oedematous, sometimes with profound systemic symptoms. In Liberia, the writer observed a native child stung by an enormous swarm of bees, which succumbed quickly before it could be resuscitated.

Recently the suggestion has been made that bees are not uncommonly associated with allergic reactions in persons sensitive to pollen and to other substances which the bees bring into close proximity to human beings, and the term "bee allergy" has recently been discussed in medical literature.

Some reports have been made that hypersensitized persons may die of shock from bee sting following previous sensitization. In some instances, the symptoms have disappeared following the early administration of adrenalin. It has been suggested that such persons who are apt to be again exposed to the sting of bees should be desensitized by injections of filtered extracts of the whole bee made up in Coca's solution, to which phenol 0.4 per cent is added.

The bumble bee differs from the honey bee in that the sting is not cast off when stinging. Jex-Blake (1942) writes the effects of bee stings in East Africa appear to be very severe. Swarms may be met with on the roads which attack on a heroic scale. He estimates that one-half dozen or more natives are killed by bees every year. Deaths also occur in Europeans. Weak ammonia or washing soda is best for allaying the irritation. For wasp stings dilute acids such as vinegar, rather than alkalies, are recommended.

Hornets and wasps have a well developed sting and are more dreaded for their sting effect than bees. The sting of the wasp is often very painful. If the stinging apparatus of the *Hymenoptera* has been left in the wound, it is important that it should be removed with a sharp knifeblade or needle, to prevent discharge of additional venom from the poison reservoir. If the individual has been stung by many wasps, and systemic shock occurs, cardiac and respiratory stimulants may be advisable. Local applications and warm packs may also be employed.

It is of interest to note the report of Pawlowsky and Sondak (1936) that the wasp *Polistes gallicus* may serve as a disseminator of the eggs of *Ascaris*, *Ancylostoma*, and *Trichocephalus*, the infection being carried about on the wings, legs, body and mouth parts and not in the digestive tract.

Ants.—In temperate regions, ants rarely are considered as producing injury, but in the tropics there are large, formidable species which may not only cause local irritation, but even produce general symptoms of nervous system involvement. The large ants of Central and northern South America, particularly the tucandeira (*Paraponera clavata*) are especially feared by the natives because of the very painful lesions which follow their stings.

In parts of India and Africa, the lesions produced by the tropical foraging ants of the genus *Monomorium* are of a very different nature, being produced by the bites of the mandibles of their jaws.

In the Philippines some species of ants are prominent factors in destroying house fly larvae so that in this way they are of great assistance to man.

Caterpillars.—Certain caterpillars, of various families of Lepidoptera (moths), have hairs with poison gland cells, which irritate the skin, producing a more or less extensive rash. The caterpillars of the brown-tail moth have hairs which when shed and coming in contact with the skin cause the "brown-tail rash." Allergic reactions may be produced by venoms, scales, or other products of anthropods which may not generally be recognized as poisonous—eczemas, coryza or asthma.

Beetles.—The best known of the urticating (vesicating) beetles is *Lytta vesicatoria*, the Spanish fly, the source of cantharadin which is most concentrated in the genitalia of the beetle. Other species of the family *Meloidae* have similar properties. Certain species of the genus *Paederus* or *rove* beetles, contain a toxic principle, not cantharadin,

in their body fluids which on contact with the human skin, causes an acute vesicating lesion which heals very slowly (Bequaert, 1932; Roberts and Tonking, 1936). Certain species of dung beetles may serve as an intermediate host of *Acanthocephala* and *Gongylonema*.

Cone-nosed Bugs.—These have been discussed on page 212 (Triatomidae). The bites of certain species of *Reduvius* (kissing bug) or *Triatoma* may cause nausea, acceleration of pulse and respiration, and urticaria. Species of *Rasahus* (Corsairs) are noted for the severity of their bite, which is often attended with cellulitis, followed by bacterial infection and possible septicaemia. A species *R. bigguttatus* is found in the Western United States.

Poisonous Fish

Fish Poisonous as Food.—Illness produced by eating decomposed fish, whether in the natural state or canned, belongs to the general problem of

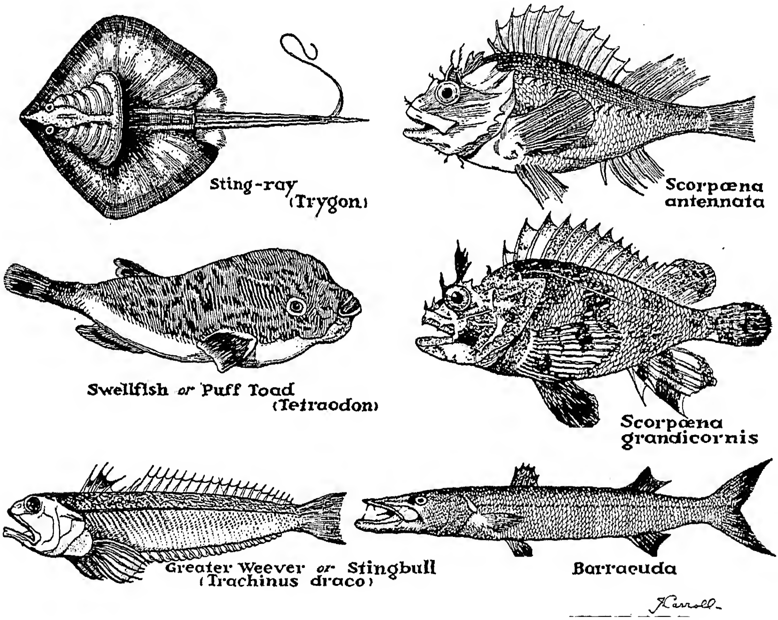

FIG. 390.—Poisonous fishes.

food poisoning. There are, however, certain fish whose meat is poisonous when eaten in a perfectly fresh state.

This may be connected with certain epidemic diseases among fish that are ordinarily harmless as food. Various bacterial organisms have been isolated from such fish, and the poisonous effects have been attributed to various ptomaines elaborated by these toxicogenic organisms. Most of the organisms isolated from diseased fish have belonged to the colon or proteus groups. Cases have been reported of botulism-like poisoning, arising from the eating of insufficiently salted fish. These cases were probably due to the development of a soluble toxin by *Cl. botulinus*, as such fish when cooked lost their toxicity. The toxin of *Cl. botulinus* is destroyed by heat, whereas that due to the Gärtner, or ordinary food poisoning organism, withstands ordinary cooking temperatures. This fiish poisoning by bacterial products is designated *ichthyotoxismus*.

The only two important animal parasite infections with which the eating of fish is connected are: (1) *Diphyllobothrium latum* and (2) *Clonorchis sinensis*. The broad Russian tape-worm is a rather common parasite of man in the Baltic provinces and comes from eating insufficiently salted pike and other fish infected with this larval tape-worm. The liver fluke disease of China and Japan is caused by eating various raw or insufficiently cooked fresh water fish. These fish are the secondary intermediate hosts, the primary ones being molluscs. A very small fluke of Japan, *Metagonimus yokogawai*, is transmitted by the ingestion of certain goldfish.

There are certain fish whose meat is poisonous when there is no question of decomposition or disease in the fish. The best known instance is with certain species of the genus *Tetrodon*. The illness produced by the eating of this fish is usually termed *fuguismus*, the Japanese designating such fish by the term "fugu." The poisonous principles seem to exist chiefly in the ovaries and testes, the eating of even one roe of such fish bringing on serious illness in a few minutes or possibly death in a few hours. It has been stated that after careful removal of all genital and alimentary tract organs these fish may be eaten without harm. The poisonous principle has a physiological action somewhat like curare, and is thermo-stable. Such fish have been used particularly in Japan to commit suicide.

Boesoirie (1940) has reported 9 cases in the Netherlands Indies in which the fish identified as *Tetrodon argenteus* was cooked and eaten by 4 adults and 5 children. One adult and one child died within 2 hours of the onset of symptoms.

The porcupine fishes or Diodontidae also are considered as poisonous. These fishes together with the Tetraodontidae, or broad-nosed puffers, are unsightly in appearance. Among seamen they are generally designated puff toads since they become distended with air as they are drawn out of the water. It is well recognized that certain of these fish which may fail to cause poisoning at one time may do so at another time and it is particularly noted that poisoning effects occur at the time of spawning.

In the tropics fish which may ordinarily be safe as food become poisonous as a result of feeding on certain poisonous medusae and corals.

This is probably true of the barracuda, which is eaten with impunity at most times. Yet undoubted cases of poisoning with this fish have occurred. It has also been suggested that the barracuda may be poisonous at certain times in its life, for example, during spawning, or that it is subject to a more rapid decomposition at such times.

To test reports of such poisoning, Bloedorn and Hakansson (1926) reported the eating of barracuda with safety on several occasions. This fish was one of those most commonly caught in the West Indian waters surrounding Puerto Rico. The fish, eaten on several occasions, varied from 8 to 15 pounds and one weighed 26 pounds. One of the warnings from local fishermen was that very large barracudas were not safe. Fish poisoning in the tropics from barracuda or other edible fish is probably most often due to commencing putrefaction. The writer has frequently caught and eaten barracuda off the coast of Spanish Honduras.

There are certain species of the herring family which have a bad reputation. Among these are two species of *Meletta*. In New Caledonia, *M. venenosa* causes painful cramps of the body with dyspnoea, cyanosis, cold sweats and dilated pupils and at times death. *M. theissa* of the West Indies is also a very poisonous fish.

Herre describes in the Philippine Journal of Science 1924, 60 species of poisonous and worthless fishes, of the order Plectognathi.*

Macht (1941) has investigated the toxic effects of fresh muscle juices from 65 different varieties of fish in the United States, the toxicity being studied by injections into mice, as well as by studying the effect the juices had upon the growth of *Lupinus albus* seed-

* Especially in Amazonia the carnero canderiú, a slender fish of the catfish family Pygididae may bore into the urethrea of persons when bathing and cause severe bleeding.

lings. All the fish they found in their toxic group were regarded as inedible, except the catfish and the eel.

Treatment.—In all forms of fish poisoning, after ingestion, the most efficient treatment is to immediately wash out the stomach and administer saline purgatives. The remaining treatment is symptomatic. Stimulants may be necessary to counteract symptoms of shock and injections of morphine may in some instances be necessary to alleviate the pain.

Barbour (1941) classifies poisonous fishes as follows:

Spiny fishes secreting an irritant slime which is either generally distributed over the surface of the body or, more frequently, by glands situated at the base of highly developed spines which serve to inject the poison. The Sting Rays, *Trygon*, or *Dasybatis*, are typical among *Elasmobranchs*. *Scorpaena*, *Chilomycteris* and the fresh water cat fishes, such as *Ameiurus*, are examples among *Teleosts*. In some of these the poison is very virulent. In others only slightly irritant.

In some fishes, such as *Muraena*, the poisonous slime glands occur in connection with the dentition. There are many species in this genus. In some there is a complicated poison of many ferments, virulent and with divers effects.

In other species poisoning follows the eating of the flesh. This causes a disease known in the Caribbean area as Ciguatera, symptoms of which vary with the species and the susceptibility of the individual. There is

1. Gastro-enteric form: the most frequent and benign. It may, however, result in death. With epigastric pain, headache, cramps, tenesmus, muscular droopings, nausea, vomiting, chilled extremities, syncope and erythrism, even desquamation.
2. Algide form: very rapid after eating a poisonous fish by reason of the immediate nervous symptoms, alternate paralysis and convulsions; cyanosis, coma and death.

Of 2, many cases have been reported from New Caledonia after eating a local herring (*Clupea venenosa*) and a toad fish (*Tetrodon maculatum*).

Treatment in any case is purely symptomatic in spite of many local nostrums. One should empty the digestive tract; use emetics, stomach washing, purgatives and enema. Apomorphine is useful. Stimulants should be employed to support the heart and to counteract the other symptoms of shock.

In many localities there are local laws prohibiting the sale of fishes known frequently to be poisonous. At St. Simons Bay, South Africa, ships are notified on arrival to beware of the local *Tetrodon*. In Tahiti, *Clupea thrissa* is prohibited between May and October. There are laws in Cuba and many other places prohibiting the sale of other species.

Venomosity appears in a sporadic and spontaneous manner in one genus and not in another of the same family; or in one species and not in another of the same genus; but does not appear to be individual given the same condition of age, time or year or sexual maturity.

The principal cause rests in the metabolism of the fish itself and is to be considered as the exaggeration of a normal function; the toxic function is not to be considered as a pathologic phenomenon but purely a concomitant of elimination.

The toxicity is the most active when the sexual processes are most active i.e. during the breeding season. For example the eggs are venomous in our pickerel.

In man (the human being) puerperal mania or mania during pregnancy may be considered as offering examples of autointoxication of a similar type.

streams or water falls. These breeding habits explain the "patchy" distribution of the flies.

Simulium damnosum and *S. neavei* serve as the intermediate hosts of *Onchocerca volvulus* in tropical Africa. In Central America the known vectors are *Eusimulium metallicum* (*avidum*), *E. ochraceum* and *E. callidum* (*mooseri*).

Chironomidae (Midges).—These are minute flies ranging from a length of 1 or 2 mm down to almost microscopic dimensions. The wings are narrow, shorter than the abdomen, often spotted, with the first two longitudinal veins heavy, the others indistinct. They bear hairs but no scales. The antennae are relatively long and have 13 joints. The proboscis is short. Most of the species rest with the fore legs elevated. The great majority of the species are harmless. The blood-sucking species belong to the family Ceratopogoninae, and most of them to the genus *Culicoides*. These flies usually appear in dense swarms and cause troublesome irritation and itching by their bites.

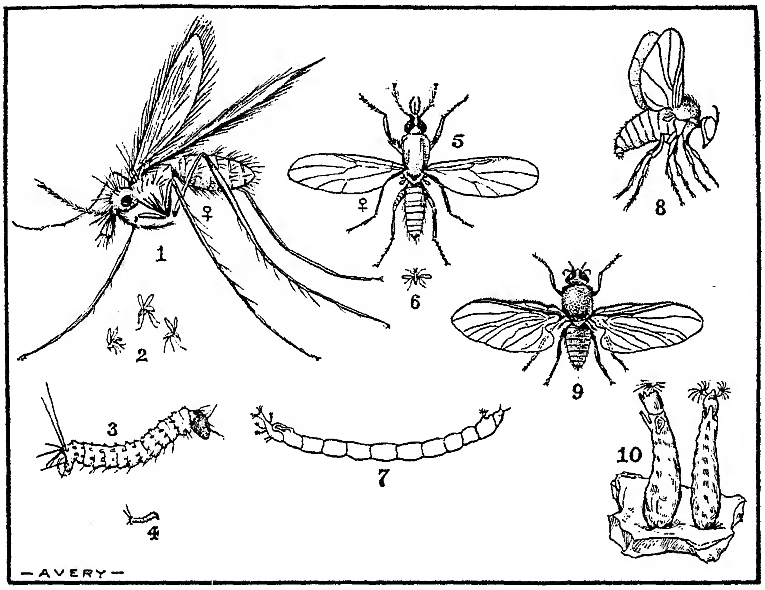

FIG. 376.—Mosquito-like insects belonging to families Chironomidae, Simuliidae and Psychodidae. (1) *Phlebotomus papatasii;* (2) *P. papatasii* (natural size); (3) *P. papatasii* (larva); (4) *P. papatasii* larva (natural size); (5) *Ceratopogon pulicaris;* (6) *C. pulicaris* (natural size); (7) *Chironomus* larva; (8) Attitude of a *Simulium;* (9) *Simulium reptans;* (10) Larvae of *Simulium.*

Culicoides grahami and *C. austeni* are the intermediate hosts of the filarial worm *Acanthocheilonema perstans* in British Cameroons. Only the females bite, and they bite only in darkness. *C. furens* was shown by Buckley (1933) to be the intermediate host of *Mansonella ozzardi* in St. Vincent. This fly, which is a troublesome biter, is found in the coastal region from Florida to Brazil.

Townsend has advanced evidence that related midges, *Forcipomyia utae* and *F. townsendi* are vectors of dermal leishmaniasis ("uta") in western Peru.

Psychodidae (Moth Midges).—These are small slender flies with very long legs. The body and wings are covered with long hairs. The wings show nine longitudinal veins which reach the margin, and cross veins only near the base. The antennae are long and hairy, and consist of 12 to 16 joints. The palpi have 4 joints. The majority of those flies have a short proboscis not adapted to biting (the Psychodinae). A relatively small group, the sand flies (Phlebotominae, genus *Phlebotomus*) are biters. They have a long proboscis, as long as the head, and mouth parts like a mosquito. The palpi

are longer than the head. The antennae have 16 constricted joints. They are further characterized by the wing venation; the second longitudinal vein bifurcates at a considerable distance from the base of the wing, instead of near the base, and has three distinct branches. When at rest the wings are raised over the abdomen at an angle of 45°. Differentiation of species is difficult and depends on slight variations in wing venation, length of the palps, etc.; thus the second segment of the palpi in *P. papatasii* is a little longer than the third; in *P. perniciosus* the segments are equal in length; while in *P. minutus* the second segment is only half the length of the third.

Phlebotomus papatasii is the vector of phlebotomus or pappataci fever. This species is abundant throughout the Mediterranean region, the Balkans, and Asia eastward to India. The flies hide in damp shady places during the day. The females emerge at night to bite man or other animals. They fly only short distances and rarely rise more than a few feet above the ground. A few days after biting they deposit their ova (40 to 60) by preference in crevices of damp shaded rocks, stone fences or ruined buildings or in caves, within one or two hundred feet of their feeding places. Occasionally they may bite a second time, and deposit a second batch of ova, but their life span is short, 7 to 14 days. The life cycle occupies 1 to 2 months. The virus of pappataci fever is acquired by biting a patient during the first day of the disease. The period of incubation in the fly is about 8 to 10 days. The virus is transmitted to the succeeding generation of flies, which appear to constitute the reservoir of the infection.

P. verrucarum and *P. noguchii* are vectors of *Bartonella bacilliformis*, the cause of Oroya Fever and Verruga Peruviana in Peru (Townsend, 1914; Noguchi et al. 1929, Hertig, 1938). Their distribution in the canyons of the western slope of the Andes corresponds closely to that of the disease.

Sand flies are probably the vectors of *Leishmania*. (See section on Leishmaniasis.) The species incriminated are: For *L. donovani—P. argentipes* in India, *P. major* var. *chinensis* and *P. sergenti* in China, and *P. major*, *P. sergenti* and possibly *P. papatasii* in the Mediterranean region (infantile and canine infections). For *L. tropica—P. papatasii* and *P. sergenti* in the Old World and probably *P. intermedius* for *L. braziliense* in South America. These species have all been infected by allowing them to bite a patient with the disease, and cyclic development of the parasite within the flies has been observed.

Man and animals have in some instances been infected by injections of suspensions of infected flies and by rubbing infected flies into the abraded skin, but not by simple biting. Crushing the fly while biting seems to be necessary to convey the infection. Only in the case of several hamsters have positive results been obtained by biting experiments with *P. argentipes* and the *Leishmania* of kala azar (Smith, Halder and Ahmed, 1940).

Harara is a disease well recognized in Palestine and has been described by Theodor as an allergic reaction due to the bites of *Phlebotomus* at the height of sensitization. Theodor studied the effect of successive bites of *Phlebotomus papatasii* on some 17 individuals not previously bitten. After the first time they were bitten, the reaction usually takes several days to develop, then intensely itching papules appear. After subsequent bites the papules appear more rapidly. The site of the preceeding bites may become inflamed again.

MacPherson (1941) reports that the men of the Australian Forces have suffered severely in North Palestine. The exposed skin becomes covered with hard weals up to 1 centimetre in diameter; these may subside or may be replaced by blisters which later may become infected, and in some cases the regional lymph glands may be enlarged and tender.

Larva Migrans.—Other names for this thread-like swelling under the skin are creeping eruption and myiasis linearis. The typical case, as occurring in Russia or South Africa, is due to the burrowing of a fly larva under the skin. The patient first notices a painful spot, which changes from day to day as the larva works its way along, at the rate of about 1 inch in 24 hours. The tract of progress is marked by a dark reddish line which terminates at an opening discharging a sero-purulent liquid and from which opening the larva escapes. The line fades as the larva progresses. The burrows may be found even on the face but more commonly on the feet or legs. The fly larvae chiefly incriminated are those of *Hypoderma* and *Gastrophilus*.

It is well recognized that other parasites than fly larvae may give rise to a creeping eruption. In *Gnathstoma spinigerum* infection there have been reported a number of cases of deamatitis due to this nematode.

content than sea-water. Fresh water mussels have an economic value in the use of their shells for button-making. Besides ill effects related to idiosyncrasy, poisoning leading to paralysis or even death may occur. In California (1927), there were reported 102 cases of mussel poisoning with 6 deaths. The symptoms developed in 10 to 20 minutes after ingestion. The toxin seems to be thermostable and is absent except during the spawning season (June through September). A few cases of poisoning, some of which were fatal, have been reported from the South Pacific due to the bites and absorption from the poison gland of Mollusks, especially *Conus geographus* (the cone shells).

Poisonous Coelenterates

In the phylum Coelenterata we find animals of very simple structure, only the sponges and protozoa having a more lowly type. It is customary to distinguish two morphological types of coelenterates, the polyp and the medusa.

The Polyp.—The best example of a poylp is a sea anemone.

Quite interesting in the study of immunity is the constant association of an anemone with certain hermit crabs. The anemone covers the soft tail-end of the crab, thus protecting the crab from attacks by its enemies. The mouths of the two animals are in close juxtaposition so that the food of the crab is shared with the anemone. This crab acquires an immunity to the poison of the anemone, probably as the result of frequent ingestion of fragments of anemone. Other crabs are very sensitive to the anemone poison, suffering paralysis and death. The poison of certain anemones may even harm other anemones.

A condition known as "la maladie des plongeurs" occurs among the sponge fishermen of the Mediterranean. This is due to stinging by anemones and is characterized by marked itching, burning and erythema. In some cases the skin of the affected area becomes necrotic and sloughs off leaving an ulcer. Levin and Behrman (1941) in the West Indies have described Coral dermatitis from the Coral polyp of the genus *Actinia*.

Species of the genus *Alstinion* and *Hellenopolypus* may, in addition to local lesions, causes nausea and vomiting. Applications of vinegar and of olive oil are recommended for its local symptoms.

The Jellyfish (*Medusa*).—This umbrella-like coelenterate has tenacles which hang down from the margin of the jellyfish.

As a rule jelly fishes are harmless but certain species produce unpleasant or even serious effects by their sting. Cases of lesions following contact with unspecified "jelly-fish" have been reported by Allen (1920) and Stewart (1922). The local rash in Allen's case was followed by profuse weeping eczema, by aphonia, and by laryngitis lasting for four weeks. Aoki (1922, 1923) portrays the severe effects, besides, urticaria, of stinging by *Olindioides formosa*—shock, acute cardiac distress, dyspnoea, muscle pains, and as a possible sequela emaciation.

In the Mediterranean a jelly fish *Rhizostoma pulini* produces oedema and urticarial eruptions as the result of its sting. In many parts of the tropics, jelly fishes are found which give rise to quite serious symptoms. In the Philippines there are certain species of jelly fishes which cause serious illness, although as a rule one experiences no discomfort from coming in contact with many other species while swimming in the waters of that part of the world.

According to Light, the species of *Dactylometra*, called "fosforo" by the natives, is the most dangerous one there encountered. It has long ribbon-like oral lappets and 24 slender white marginal tentacles. In this the sting is inflected by nematocyst batteries

in the four long ribbon-like oral palps. *Lobonema*, called by the natives "lanterna," is of large size, white or white and purple, in color, and stings by the long filaments which arise from the mouth arms. Stitt treated a number of cases of jelly fish stinging in the Phillippines which presented symptoms ranging from a mild erythema to those showing marked congestion of the respiratory tract and other general symptoms.

Old has described these symptoms very accurately and notes the following:

The symptoms appear in from ten to sixty minutes with marked hysterical manifestations, incessant cough and coryzal signs. Light believes that the cases described by Old were due to stinging by *Dactylometra*.

Wade describes his own experience with a jelly-fish sting while swimming in Manila Bay. The tentacles became wrapped about the upper arm and stinging was instantaneous as the tentacles did not cling. The poison did not reach the conjunctival or other mucous membrane. There was at once a sensation of burning in the area of contact, but it was 15 minutes before other symptoms appeared. There was pain in the loins and also in the scrotum. This was followed by a curious restlessness and weakness, then a sense of constriction in the throat, with chest discomfort and then coryza and lachrymation. The symptoms abated and within an hour there only remained weakness and soreness of the bronchi. A vesicular dermatitis appeared on the arm and the traces of the sting had not disappeared after 2 or 3 weeks.

Other cases have been reported associated with feeble heart action and semi-conscious states. There is always to be considered the possibility of one's drowning when in the emotional or semi-conscious state. Wade describes a death in a robust Filipino who was stung on the leg. His companions were only a few yards away, but by the time they had reached him he had collapsed and was gasping and livid, and was dead a few moments later. It was at first thought he had been bitten by a sea-snake but there was no mark on the leg, except conspicuous purplish discoloration. On autopsy he showed status lymphaticus with persistent thymus, acute congestion of the viscera and oedema of the lungs.

The Portuguese man-of-war (*Physalia*) has long locomotive tentacles which stretch out from 30 to 50 feet as the animal is blown along by its pearly purple crested bladder-like float or sail. The thread cells are capable of inflicting rather painful stings when handled without a knowledge of the effect of coming in contact with these thread cells.

Along the coast of eastern Florida, there are occasions when great swarms of a small, very dark brown *Medusa* occur near the shore. These are about the size of a shilling, now called *Linuche unguiculata*. It was formerly better known as *Linerges*. This species is so abundant that very severe stinging occasionally occurs, the symptoms being similar to those described above.

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Chapter LIII

TABLE OF IMPORTANT ANIMAL PARASITE DISEASES

Classification of Animal Parasites

(According to Stiles)

1. Unicellular animals (without tissues), as the parasites of malaria.........Protozoa
   Pluricellular animals (with tissues); metazoa.................................... 2
2. Body more or less flattened dorso-ventrally.. 4
   Body ordinarily round in transverse section.. 3
3. Body never annulated; never provided with legs; jaws absent.................. 5
   Body annulated, or at least provided with mouth parts; usually breathe through a tracheal system; adults with jointed legs or other appendages.............. 7
4. Intestine, but no anus, present; one or two suckers present; body not segmented; parasitic in liver, lungs, blood, intestine, occasionally elsewhere; flukes........ Trematoda

   Intestine absent; two or four suckers on head; body of adults segmented; tissue usually contains calcareous corpuscles; adults (tapeworms) parasitic in intestine; larvae (bladder worms) parasitic elsewhere.....................Cestoda
   Intestine and anus present; sucker on posterior end; body annulated like an earthworm; parasitic in upper air passages, or externally; leeches, blood suckers.... Hirudinea

5. Intestine absent; armed rostellum present; very rare in man, in intestine; thorn headed worms..................................Acanthocephala
   Intestine present; no armed rostellum............. ....Nematoda 6
6. Intestine rudimentary in adults; lateral chords absent; rare, accidental parasites in intestine of man; hair snakes or horse-hair worms...............Gordiacea
   Intestine present; lateral chords present; parasitic in intestine, muscles, lymphatics, etc., very common and important; roundworms..............Eunematoda
7. Six legs present in adult; wings present in most species; larva annulated much like an earthworm; breathe through trachea; adults ectoparasites; occasionally larva is parasitic under skin, or in wounds, or an accidental parasite in the intestine or bladder; insects..................................Insecta
   Eight legs present in adult, six legs in larva; head and abdomen coalesced; ectoparasites; some burrow under the skin or live in the hair follicles; acarines...... Acarina

   Four claws around the mouth; larva encysted in various organs; adult occasionally parasitic in nasal passages; tongue worms................Linguatulidae
   Numerous legs present; occasionally accidental parasites in nasal passages or intestine; thousand leggers. .Myriapoda

Diseases Caused by Protozoa

Parasite	Defin. host	Intermediate host	Important reservoir of virus	Transmission and pathogenicity
Endamoeba histolytica.	Man.	Not required.	Man-carrier stage (faeces).	Cysts in food or water. Flies may act as carriers. Ingestive. Amoebic dysentery.
Balantidium coli.	Man (hogs).	Not required.	Man-carrier stage (hogs).	Transmission probably same as for E. histolytica. Ingestive. Balantidium dysentery.
Giardia lamblia (Lamblia intestinalis).	Man.	Not required.	Man-carrier stage (mice and rats?).	Transmission probably same as for E. histolytica. Rat faeces on human food important. Ingestive. Lamblia dysentery. Giardiasis.
Trypanosoma gambiense and rhodesiense.	Fly (Glossina species).	Man.	Man—game animals? (blood).	Cyclical development in tsetse fly. Inoculative. Sleeping sickness.
Trypanosoma cruzi.	Triatoma megista and related insects.	Man.	Man.	Cyclical development in bug. Inoculative. Brazilian trypanosomiasis.
Leishmania donovani, infantum, tropica and braziliensis.	Not surely known.	Man.	Man.	L. donovani—probably transmitted by various species of Phlebotomus—kala-azar. L. infantum—infantile leishmaniasis. L. tropica—Oriental sore. L. braziliensis—American leishmaniasis.
Plasmodium malariae, vivax and falciparum.	Mosquito (Anopheline species).	Man (with schizonts).	Man blood) (with gametocytes).	Cyclical development in mosquito—12 days. Inoculative. Malaria.

DISEASES CAUSED BY PARASITES FORMERLY CONSIDERED PROTOZOA

Parasite	Defin. host	Intermediate host	Important reservoir of virus	Transmission and pathogenicity
Borrelia recurrentis, carteri, etc. (Louse group).	Louse (P. humanus, var. corporis.)	Man.*	Man (blood).	Cyclical development in louse. Bite puncture contaminated by crushed louse. Relapsing fever.
Borrelia duttoni, novyi. (Tick group.)	Tick (species of Ornithodorus or Argas).	Man.*	Man (blood).	Excretions of tick contaminating tick-bite, Tick fevers. Relapsing fever.
Treponema pallidum and pertenue.	Man.	Not required.	Man.	T. pallidum. Usually venereal. Syphilis. T. pertenue. Flies or contact. Yaws.
Leptospira icterohaemorrhagiae.	Man (rat).	Not required.	Rat.	Common infection of rats. Present in blood. Excreted in urine. Ingestion. Weil's disease.
Leptospira morsusmuris.	Man (rat).	Not required.	Rat.	Man inoculated by bite of infected rat. Rat bite fever.
Rickettsia prowazeki.	Man.	Louse (P. humanus, var. corporis.)	Man (blood).	Cyclical development in louse. Bite puncture inoculated by louse faeces. Typhus fever.
Rickettsia rickettsi. (Dermacentroxenus rickettsi.)	Man (goats, rodents. etc.).	Tick (Dermacentor andersoni).	Goats and rodents.	Excretions of tick contaminating tick bite. Rocky Mountain spotted fever.
Rickettsia tsutsugamushi.	Man.	Larvae Kedani mite (Trombicula akamushi)	Field mice.	Trombicula akamushi. Tsutsugamushi disease.
Bartonella bacilliformis.	Man.	Species of Phlebotomus.	Man (blood).	Transmitted by species of Phlebotomus. Inoculative. Carrion's disease.
Filtrable virus of yellow fever.	Aedes mosquitoes.	Man.	Man (monkeys).	Cyclical development in mosquito. Inoculative.
Filtrable virus of dengue fever.	Aedes mosquitoes.	Man.	Man.	Cyclical development in mosquito. Inoculative.
Filtrable virus of pappataci fever.	Phlebotomus.	Man.	Fly.	Cyclical development in fly. Inoculative.

Note.—Although these diseases are caused by parasites which are now classified with the bacteria or in an intermediate group, or are due to filtrable viruses, they have been retained in this table because they resemble protozoal diseases, particularly in the mode of transmission and in the life cycle of the causative agents.

* *Some authorities regard man as the definitive host of Borrelia.*

Helminthic Diseases—Trematodes

Parasite	Defin. host	Intermediate host	Important reservoir of virus	Transmission and pathogenicity
Clonorchis sinensis.	Man (cats, dogs, hogs, rarely some rodents.	1st, snail (species of Parafossarulus and Bythinia) and 2d, fish.		Eating raw fish. Ingestive. Human liver fluke disease.
Opisthorchis felineus.	Man (cats dogs and hogs).	1st, mollusc. (Bithynia tentaculata. 2d, fish.	Cats and dogs.	Man probably infected by eating raw fish. Ingestive. Liver fluke disease.
Fasciolopsis buski.	Man (pig).	Species of Planorbis and Segmentina.	Hog.	Ingestion of cercariae encysted on water plants. Intestinal Distomiasis.
Heterophyes heterophyes.	Man (dogs and cats).	1st, Pironella conica and probably other snails. 2d, fish.	Dogs and cats.	Ingestion of raw fish. Intestinal Distomiasis.
Paragonimus ringeri.	Man (dogs, cats, domestic and wild, hogs).	1st, snail (species of Melania) 2d, crab.	Cats, dogs and hogs.	Eating raw crabs containing cercariae. Ingestive. Lung fluke disease.
Schistosoma haematobium.	Man.	Snail (species of Bulinus, Physopsis and probably Planorbis.	Man (urine).	Bathing or drinking water containing cercariae. Penetrative. Vesical bilharziasis.
Schistosoma mansoni.	Man.	Snail (species Planorbis (Australorbis) and Physopsis, and possibly others.	Man (faeces).	Bathing or drinking water containing cercariae. Penetrative. Rectal bilharziasis.
Schistosoma japonicum.	Man.	Snail (species Katayama, Oncomelania and probably Schistosomorpha.)	Man (faeces) (domesticated animals).	Bathing or drinking water containing cercariae. Penetrative. Katayama disease.

Note.—Rare trematodes of man include: (1) *Fasciola hepatica;* (2) *Dicrocoelium dendriticum;* (3) *Metagonimus yokogawai;* (4) *Echinostoma ilocanum;* (5) *Watsonius watsoni;* (6) *Gastrodiscus hominis;* (7) *Troglotrema salmincola.*

Helminthic Diseases—Cestodes

Parasite	Defin. host	Intermediate host	Important reservoir of virus	Transmission and pathogenicity
Diphyllobothrium latum.	Man.	1st, Cyclops strenuus and Diaptomus gracilis. 2d, fish.	Man (faeces), dog, cat and bear.	Eating raw fish containing plerocercoid larvae. Broad Russian tape-worm disease.
Diphyllobothrium mansoni.	Dogs, cats, other carnivores.	1st, cyclops. 2nd, frog, snake, rarely man.	Frogs.	Ingestion of cyclops?. Application of raw frogs to ulcers. Cysts in subcutaneous tissues, often in orbit.
Hymenolepis nana.	Man. Rat.	Not required.	Children (faeces). Rat.	Man intermediate and definitive host. Ingestive. Dwarf tapeworm disease.
Hymenolepis diminuta.	Man and rat.	Rat fleas and other arthropods.	Rat.	Cases occur rarely in children. Probably ingestion of rat flea.
Taenia saginata.	Man.	Cattle.	Man (faeces).	Eating insufficiently cooked beef containing cysticerci. Ingestive. Beef tapeworm disease.
Taenia solium.	Man.	Hog. (Rarely man.)	Man (faeces).	Eating insufficiently cooked pork containing cysticerci. Ingestive. Pork tapeworm disease.
Echinococcus granulosus.	Dog and other carnivores.	Man, cattle, sheep and hogs.	Dog (faeces).	Dogs infected at abattoir. Hydatid disease.

Note.—Rare cestodes of man include: (1) *Dipylidium caninum;* (2) *Species of Davainea;* (3) *Drepanidotaenia lanceolata;* (4) *Multiceps multiceps (coenurus stage);* (5) *Sparganum proliferum;* (6) *Diplogonoporus grandis;* (7) *Bertiella studeri.* (*See text.*)

Helminthic Diseases—Nematodes

Parasite	Defin. host	Intermediate host	Important reservoir of virus	Transmission and pathogenicity
Wuchereria bancrofti (Filaria bancrofti).	Man.	Mosquito (various species).	Man infected (blood).	Indirect in mosquito. Mature larva penetrates skin. Elephantiasis, etc.
Loa loa (F. loa).	Man.	Species of Chrysops (mangrove) flies).	Man infected (blood).	Indirect (cyclical) in Chrysops. Probably inoculative. Ocular filariasis, etc.
Mansonella ozzardi.	Man.	Culicoides furens.	Man.	Indirect in Culicoides. Inoculative. Non-pathogenic.
Acanthocheilonema perstans (F. perstans).	Man.	Species of Culicoides.	Man infected (blood).	Transmission by Culicoides. Non-pathogenic.
Dracunculus medinensis.	Man.	Species of cyclops.	Man infected (subcutaneous tissue).	Larvae enter cyclops. Infected cyclops in drinking water. Ingestive. Guinea worm infection.
Onchocerca volvulus (Filaria volvulus). (O. caecutiens.)	Man.	Species of Simulium.	Man. (Lymph spaces of skin.)	Simulium flies. Inoculative. Subcutaneous tumors and lymphangitis. Blindness.
Strongyloides stercoralis.	Man.	Not required.	Man (faeces).	Parasitic filariform larva penetrates skin. May cause severe diarrhoea.
Necator americanus and Ancylostoma duodenale.	Man.	Not required.	Man (faeces).	Strongyloid larvae penetrate skin. Ancylostomiasis.
Trichinella spiralis.	Man (rat and hog).	(Hog (man and rat).	Hog (muscle).	Encysted larva in raw or insufficiently cooked pork. Ingestive. Trichinosis.

Note.—Ascaris, Trichuris and Enterobius (Oxyuris) do not require intermediate hosts. With Ascaris and Trichuris, larva gradually develops in egg passed in faeces. Infection by ingestion of embryo-containing eggs. Embryo-containing eggs contaminate fingers from crushing female Enterobius in perineal region.

Arthropodan Diseases

Parasite	Life history	Disease and manifestations and remarks
Linguatula serrata (Linguatulidae).	Adult in nasal cavity of dogs, etc. Eggs in nasal mucus contaminate grass. Rabbits, cattle infected. Larvae in liver, lungs.	Porocephaliasis. Man may harbor larva, rarely adult. Larvae usually in lungs or liver and do not seem to cause symptoms.
Armillifer armillatus (Linguatulidae).	Adults in lungs of snakes. Eggs contaminate water or food. Larvae in liver, lungs, etc., of lions, monkeys, rats, man, etc.	Porocephaliasis. Larvae in liver, lungs and other organs.
Demodex folliculorum (Demodicidae).	All stages passed within hair follicles or sebaceous glands, especially about nose. Adult may wander.	Demodectic acariasis. Causes a resistant itch in dogs. In man, may invade eyelids or Meibomian glands, but appears to be harmless.
Sarcoptes scabiei (Sarcoptidae).	Female lives in burrow of skin giving off eggs which hatch into larvae.	Scabies. Burrows show as blackish lines, especially between fingers, flexor surface of arms and penis. Itching worse at night.
Pediculoides ventricosus (Pediculoididae).	Female lives on wheat-straw worm or grain moth. Larval mites develop inside mother.	Grain itch. The mites leave wheat straw or grain and attack harvesters or those sleeping on straw mattresses. Attack upper trunk, neck and arms. Erythematous or vesicular eruption with constitutional symptoms.
Trombicula irritans (Trombidiidae).	Adults live in fields or woods. The larval mite lives on grass-hoppers or small rodents.	Autumnal erythema. The larval mites known as harvest mite, red bug or jigger attack man causing a severe itch.
Dermanyssus gallinae (Parasitidae).	Mites live in chicken houses and feed on fowls.	Poultryman's itch. The mites attack man producing eczematous dermatitis on backs of hands and forearms.
Liponyssus bacoti.	Tropical rat mite. May bite man.	Conveys endemic typhus to man in southern U. S. The rickettsiae are transmitted to the eggs.
Glyciphagus domesticus (Tryoglyphidae).	Mites found in flour and sugar.	Grocer's itch.
Dermacentor andersoni (Ixodidae).	Adults live on cattle, sheep, etc. May bite man.	Tick paralysis. The bite of this tick or species of Ixodes may produce paralysis in sheep. An ascending type of paralysis due to tick bites has been several times noted in man, chiefly in children.
Pediculus humanus, var. corporis (Insecta, Pediculidae).	Adults live on clothing or hair and feed on man.	Pediculosis—Phthiriasis. Produce skin irritation with (later) pigmentation (Vagabondismus).

ARTHROPODAN DISEASES.—(*Continued*)

Parasite	Life history	Disease and manifestations and remarks
Tunga penetrans (Dermatophilus penetrans) (Tungidae).	Impregnated female penetrates skin of man or animals.	Sandflea or chigoe infestation. Site of penetration shows as black spot with whitish induration surrounding it. Apt to form ulcers.
Dermatobia hominis (Oestridae: Bot Flies)	Eggs of fly become attached to mosquitoes or ticks. These latter bite man and larva penetrates skin.	A cutaneous myiasis. Larva at first club-shaped (ver macaque). Later worm-shaped (torcel). Larva causes a swelling with black opening. May invade eye.
Hypoderma lineata, Gastrophilus nasalis (Oestridae).	Larvae of these or other flies burrow under skin.	Creeping eruption. Larva migrans. The burrows make zigzag lines on face or soles of feet. Causes itching.
Cochleomyia americana Chrysomyia bezziana (Muscidae). Oestrus ovis (Oestridae).	Fly deposits eggs in nostrils, ears or open wounds. Larvae wander to nasal sinuses. May invade aural canal.	Screw-worm infection. Nasal myiasis. Larvae in their wandering destroy tissues of nasal cavities, or of ear, and may cause death. May infest wounds or vagina. C. americana causes American nasal myiasis, C. bezziana causes Indian nasal myiasis and O. ovis causes African nasal myiasis.
Cordylobia anthropophaga (Ochromyia anthropophaga) (Muscidae).	An African fly which deposits eggs on clothes or sand. Larvae (African skin maggot) attack children or small animals.	Larvae bore under skin, causing boil-like lesions with central opening. Larvae mature in two weeks.
Auchmeromyia luteola (Muscidae).	An African fly; deposits eggs on floors of native huts. Larvae bite man.	Congo floor maggot. The bite is not painful.
Calliphora vomitoria, Lucilia caesar, L. serricata (Muscidae). Phormia regina, Cochleomyia macellaria and C. americana.	Blow and green-bottle flies, depositing eggs on tainted meats. Larvae may be found in faeces.	Larvae may be cause of intestinal myiasis; may be found in nasal cavities or in skin wounds causing serious symptoms, or in ear.
Musca domestica (Muscidae).	Eggs presumably deposited near genitalia or ear.	Larvae have been found in male urethra and in the ear and in the intestinal tract.
Sarcophaga carnaria, Wohlfhartia vigil (Sarcophagidae).	Viviparous. Larvae are deposited on decaying flesh (wounds, orifices of body).	Larvae gain access to wounds, nasal cavities, etc., at times causing death. Commonly found in intestinal myiases. May occur in vagina.
Anthomyia pluvialis (Anthomyidae).	Larvae deposited in body orifices.	Occasionally reported as found in ear.
Fannia canicularis (Anthomyidae).	Eggs deposited near external genitalia and larva penetrates urethra.	Symptoms of urinary irritation or obstruction. Has been found in gastrointestinal tract.

SECTION VIII

GENERAL AND STATISTICAL CONSIDERATIONS

Chapter LIV

PROBLEMS OF MEDICAL PRACTICE IN THE TROPICS: COSMOPOLITAN DISEASES IN THE TROPICS

In the diagnosis of infectious processes in temperate climates one often keeps in mind syphilis, tuberculosis and the pyogenic infections when the diagnosis is in question. In the tropics these conditions are just as common, and added to them we encounter many other diseases with protean manifestations as in malaria, beriberi, leprosy, ancylostomiasis and other helminthic infections, pellagra and amoebiasis.

A common mistake that may be made by the physician when he first arrives in a tropical country is to expect to deal chiefly with diseases designated tropical. Before going to any tropical country a most important preparation is the study of statistical reports from that section, covering a number of years. However, such records are often not to be found. Everyone taking up the study of tropical disease should study the geographical distribution of such diseases, and those practising in temperate climates should remember that one of the first questions to be asked a man suspected of having a tropical disease is "Where have you been during the past months and years?" Then too it is often advisable to apply the same question to intimate associates of the patient.

While a medical man is apt to have superabundant energy during the first few months of his tropical service, this later may give way to the opposite state and in particular to a lack of initiative. It may be possible to do that which is absolutely demanded in the daily work, but one may feel that beyond the lines of routine requirements it is difficult to undertake new investigations and the more difficult procedures for diagnosis.

Consequently, while in possession of full energy and zeal one should formulate a method or system of history taking and physical examination applicable to the diseases prevalent in the country in which he is working and make this a routine procedure.

The close observer will note at a glance such obvious clinical manifestations as skin pigmentation, eruptions, ulcers, malformations, emacia-

tion, dyspnoea and many other outstanding signs of disease. Logical deduction from such observations will often suggest the proper laboratory procedures to follow in order to make an accurate diagnosis.

The general examination of the patient may be based upon the anatomical plan, examining one portion of the body at a time; or the physiological examination of the organs by systems. Either plan should be followed by a more detailed examination of the system or part of the body which seems to be principally at fault. After such an examination, one is in a position intelligently to outline definite laboratory procedures. The accumulated evidence obtained by observation, history, physical examination and laboratory data is then considered and a provisional diagnosis arrived at. Diagnosis will be confirmed or denied by further study, additional laboratory aid or progress of the patient. There are many pitfalls in the way of the diagnostician in the tropics and one should approach each new patient with an open mind and especially guard against becoming possessed of fixed ideas, or the making of "snap diagnoses."

We all know how difficult it is in temperate climates at times to find definite pathological conditions in people who complain of illness and yet who are apparently well. In such patients a definite finding of a cause sufficient to account for an illness is usually the key to the diagnosis. With those from the tropics, however, it may be different. Thus a single individual exceptionally may be found upon examination to have amoebiasis, malaria, filariasis and syphilis, yet none of these infections may prevent him from following his usual occupation. When such a patient enters a hospital ward it requires a correlating mind to eliminate four or five definite diseases, and to recognize in addition some disease which is also existent and common to both tropics and temperate climates, as for example, typhoid fever.

In diagnosis in the tropics it is important to have a knowledge of the various physical signs and subjective symptoms more or less characteristic of every disease of man as well as of the procedures necessary for laboratory diagnosis. Often it is only when one has assembled all obtainable information that the solution of the medical problem becomes possible.

Furthermore, it is necessary to be familiar with the fact that certain infections, which at times give rise to marked alterations in the health of a patient, may at other times, and in particular when different races of man are concerned, give rise to no recognizable interference with health. This is particularly true of certain helminthological diseases, as for instance the slight effects often noted in hookworm infection in the African races as against the marked damage to those of the white race harboring such parasites.

We do not always fully appreciate the assistance the history of the present illness as well as personal and family history of a patient may give us, although it is generally recognized as the first line of approach in diagnosis. In the tropics, when dealing with natives, we may have the difficulty of language to contend with as well as with native superstition

and popular ideas as to nature and causation of disease. When employing a native interpreter it is always well to keep in mind the fact that such assistants will rarely admit of ignorance of the language to the medical man and, furthermore, they try to twist the answers of the patients to make them agree with what they may think is in accordance with the desire of the examiner. In many parts of the tropics, the history obtained from the patient in regard to his age is often very untrustworthy. Again in carrying out the physical examination it is difficult to be certain that the findings as to location or degree of pain, sensations, or time of appearance of lesions, as well as data as to pulmonary, renal and alimentary tract disorders, are correct.

It is not difficult in some localities to train a native helper to make and stain correctly good blood films as well as to examine such preparations, and the same holds for preparations of the urine and faeces. The skill in making preparations, the familiarity with pathological findings and the patience in studying a preparation on the part of these assistants is at times a matter of surprise. In regard to the intelligent and reliable examination of such preparations it is advisable for the physician to confirm the diagnosis himself by having the native attendant demonstrate any parasites he may encounter.

It has been emphasized that tropical diseases do not necessarily predominate in most tropical countries. Many important infectious diseases are characterized by their cosmopolitan nature. The prevalence of some of these is often modified by a tropical environment.

Stitt made a valuable statistical study of the cases reported from the hospitals of the United Fruit Company located in Cuba, Jamaica, Colombia, Panama, Costa Rica and Honduras. In order to contrast disease prevalence in the tropical part of the new world with that of the Orient, he selected the figures of the Philippine General Hospital as affording statistics which may be accepted as particularly reliable, in view of exceptional opportunities for accuracy in diagnosis afforded that hospital by reason of its close affiliation with the Philippine Bureau of Science.

The statistical reports recorded in the table of the cases of the hospitals of the United Fruit Company are for the year 1927, and in the returns of the Philippine General Hospital for the year 1924.

The United Fruit Company in 1927 employed in its tropical stations approximately 2000 white persons and 52,500 colored persons. Including members of families and non-employees, the medical department had supervision over, or direct contact with, 140,400 persons. During the year, 26,763 patients were treated in its hospitals and 150, 863 in hospital dispensaries. Including hospitals, dispensaries, and field dispensaries, 238,117 persons were treated during the year. The death rate among white employees was 5.65 per thousand, and for colored employees, 9.98 per thousand.

According to these statistics, pneumonia, diseases of the heart and arteries, tuberculosis, cancer, and acute and chronic nephritis were among the chief causes of death. In normal labor, no death occurred in 368

Disease	United Fruit Company			Philippine General Hospital Manila, P. I.		
	Hospitals		Out patients	Hospital		Out patients
	Cases	Deaths	Cases	Cases	Deaths	Cases
Endemic or infectious diseases						
Malaria	7,858	60	26,499	443	23	727
Influenza	726	2	7,893	376	5	716
Dysentery (total)			2,799	....		253
Amebic	424			87		
Bacillary	23			59		
Unclassified	91			18		
Veneral infections	1,728		8,377	73		376
Other endemic or infectious diseases	.....		1,079			
Hemoglobinuric fever	140	37				
Smallpox	0	0				
Measles	11					
Scarlet fever	0					
Whooping cough	2			19		
Diphtheria	6			1		
Mumps	11			4	0	
Leprosy	5			4	0	49
Erysipelas	66			11	0	15
Acute poliomyelitis	1	0				
Epidemic cerebrospinal meningitis	7	4		28	17	
Varicella	14	0		1	0	
Rubella	1	0				
Dengue	4	0				
Yaws	81	0				
Purulent or septicemic infection	45	31		75	46	
Glanders	0	0		0	0	
Tetanus	13	9		24	12	
Tuberculosis of respiratory system	287	62		683	93	1,544
General diseases						
Cancer	75	23	61	193	23	180
Tumors (not malignant)	47	0	94	90	4	265
Acute and chronic rheumatism and gout	299		4,147	73		234
Anemia, chlorosis						
Anemia, acute (secondary)				12	7	
Anemia, aplastic				1	0	
Anemia, secondary				23	0	
Anemia (secondary)				247	42	
Anemia, severe				21	9	
Banti's disease				4	0	
Banti's (secondary)				1		
Pernicious anemia	7					
Other anemias not otherwise specified	225		2,031			432
Other general diseases			1,430			
Scurvy				10	3	0
Pellagra	2			0	0	0
Beri-beri	32			155	19	435
Rickets	0			2	1	2
Diseases of thyroid gland	8			64	1	117
Leukemia and Hodgkin's disease	1			5	2	6
Alcoholism, acute and chronic	31			4	0	0
Autointoxication	22				0	
Diseases of the nervous system and organs of special sense						
Diseases of the nervous system			2,785			
Encephalitis	7	1		13		3
Meningitis (non-epidemic)	31	19				
Progressive locomotor ataxia	8	3		5		0
Myelitis	3	0		1		
Cerebral hemorrhage, apoplexy	10	8		37	27	9
Paralysis (without specified cause)	34	4		31	4	45
General paralysis (of insane)	1	1		20	0	9
Other forms of mental alienation	27	0		22	2	6
Epilepsy	19	1		21	0	33
Infantile convulsions	8	5		1	1	0
Hysteria, neuralgia, and neuritis	137	0		176	0	809
Diseases of the organs of vision and adnexa	458	0	3,347	479	5	4,707
Diseases of the organs of hearing and the mastoid processes	145	0	1,105	108	8	1,629

Disease	United Fruit Company			Philippine General Hospital. Manila, P. I.		
	Hospitals		Out patients	Hospital		Out patients
	Cases	Deaths	Cases	Cases	Deaths	Cases
Diseases of the Circulatory System						
Organic diseases of heart			479			
Other diseases of circulatory system			1,347			
Acute endocarditis and myocarditis	17	7		36	28	37
Other diseases of heart	166	35		607	165	283
Diseases of the arteries, atheroma, aneurysm, etc	40	3			15	9
Embolism and thrombosis	3	1			3	0
Diseases of the veins	90	0		195	4	240
Diseases of lymphatic system	320			63	3	428
Hemorrhage, other disease of circulatory system				67		
Diseases of Respiratory System						
Bronchitis (acute and chronic)	614		7,654	413		1,954
Pneumonia and pleurisy			428			
Broncho-pneumonia	128	37		376	136	432
Pneumonia	341	109		122	40	18
Pleurisy	131	5		171	19	204
Other diseases of respiratory system						
Gangrene of the lung				0	0	0
Asthma				42	0	188
Diseases of the Digestive System						
Diseases of mouth and adnexa	210		2,518	115	6	6,706
Diarrhea and enteritis	259		2,326	268	67	1,211
Ancylostomiasis	643		1,213	129		21
Other diseases of digestive system	....		14,399			
Diseases of pharynx and tonsils	262			1,053		2,109
Ulcer of stomach and duodenum	31			86		322
Diseases due to intestinal parasites	146			695	30	483
Appendicitis and typhlitis	154			1,425	13	1,057
Hernia, intestinal obstruction	179			129	13	113
Other diseases of intestines	113			149	33	691
Acute yellow atrophy of liver	3			0	0	0
Cirrhosis of the liver	30			44	12	6
Biliary calculi	16			25	5	0
Other diseases of liver	163			258	44	440
Abscess of liver	11			9	4	
Non-veneral Diseases of the Genito-urinary System and Its Adnexa			4,026			
Acute nephritis	44	7		89	47	88
Chronic nephritis	161	35		187	83	182
Chyluria	0	0		0	0	0
Calculi of urinary passage	7	0		40	0	107
Diseases of the bladder	71			242	25	250
Diseases of urethra, urinary abscess	115			45	1	78
Diseases of the prostate					3	14
Cysts and other benign tumors of ovary	26			104	5	50
Salpingitis or pelvic abscess	104			161	9	161
Benign tumor of uterus	35			55	2	48
Non-puerperal uterine hemorrhage	12					23
The Puerperal State						
Puerperal hemorrhage	7				11	9
Other accidents of childbirth	76			342	22	125
Childbirth (normal)	368			1,574	3	
Diseases of Skin or Cellular Tissue						
Boil, carbuncle, furuncle	213		2,869	93	6	578
Phlegmon, acute abscess	777		5,159	334	26	2,117
Other diseases of the skin and its adnexa	1,330		14,766	486	33	
Diseases of Early Infancy			104			
Congenital debility, icterus, and sclerema				204	16	
Old Age (senility)			19	2	2	

cases in the United Fruit Company's hospitals and but in 3 in 1574 cases at the Philippine General Hospital.

Notable among diseases important from an economic standpoint, are venereal diseases, malaria, filariasis, yaws, and hookworm infections, which have a distinct bearing upon mortality rates without being a direct cause of death. The annual mortality rate among the inmates of Bilibid Prison in Manila was reduced from about 238 per thousand to about 75 per thousand by general sanitary measures. After the prisoners began to be systematically treated for intestinal worms, the death rate was further reduced to 13.5 per thousand (Heiser, 1908). However, this reduction was not alone due to the removal of the helminthic infections but to other general sanitary improvements made in the prison life, improved diet, etc.

In connection with the statistics of the Philippine General Hospital, it should be mentioned that cases of leprosy, cholera, plague and small pox in Manila were sent to special hospitals for these diseases and not to the Philippine General Hospital. The number of cases in any year of such diseases as cholera or plague would depend upon the size of an outbreak or epidemic.

In the table above, it may be noted that no case of scarlet fever was recorded. Diphtheria, measles, and cerebrospinal fever, while showing a preference for cold weather, prevail in tropical as well as temperate climates. It is interesting to note that no case of pellagra was reported by the Philippine General Hospital and that while fewer cases of beriberi were treated in the United Fruit Company's hospitals, the disease was present in both localities.

Choisser, working in Haiti, found that in 300 autopsies tuberculosis was found to be the cause of death in 99 cases, syphilis in 9, and cancer in 7. Of 210 patients coming from all parts of the Island during 1927, cancer was found in 38.

A few of the important cosmopolitan diseases are referred to alphabetically below.

Alimentary Tract.—Acute appendicitis in Indians, both among Moslems and Hindus has been reported as exceedingly rare. Manson-Bahr (1940) has seen only 2 cases in an experience of over 30 years. He also emphasizes that inflammation of the appendix is rare in native races generally and that fulminating cases requiring immediate operation seldom occur, in marked contrast to the frequency in European residents. On the other hand, the statistics given in the table show 154 cases in Central America and 1425 cases in Manila, the greater proportion in natives. Probably the great majority of natives in the tropics, especially those living in rural communities, who suffer attacks of appendicitis either recover or succumb without ever applying to a physician or surgeon for treatment.

The occurrence of appendicitis in connection with helminthic infections is referred to in the chapter XLIII on cosmopolitan nematodes and in the chapter on schistosomiasis, XLVII.

Gastric Ulcer.—DeLangen (1936) has collected statistics showing the rarity of gastric ulcers among the natives in some countries. As a result of 2170 autopsies, Kouwenaar came to the conclusion that ulcers of the

stomach and duodenum are found in only 1 per cent of the male Javanese and 0.95 per cent of the female, against 10.1 per cent amongst the Chinese and 5.6 per cent amongst the Klings. Bonne, in 1338 autopsies on natives in Netherland India, found gastric ulcers only 5 times (0.37%) and duodenal ulcers only 8 times (0.63%). Of the 5 patients with gastric ulcers, 4 were suffering at the same time from a severe grade of tuberculosis and the appearance of the ulcers led one to think that they might also have been tuberculous in origin. Among 541 autopsies of Chinese in the same period of time, gastric ulcers were found 16 times: that is a percentage of 3 per cent, which figure agrees with some of the figures found in European statistics.

Castellani reports in his book that in his years of practice in various parts of the tropics he only saw 2 cases of gastric ulcer among the native races. McGarrison in Hunza in the Himalayas never saw a single sufferer from gastric ulcer. In Bengal, on the other hand, in other words in the heart of tropical British India, many sufferers with gastric ulcers are met with, according to Houston.

Pel, in Egypt, seldom observed gastric ulcers. From the annual reports of South Africa, it would appear that gastric ulcer is also quite infrequent among the coloured races of that part of the world. The same applies to the Belgian Congo. On the other hand, reports from Abyssinia show that this disease is by no means uncommon there, while the same is reported of several negro races living in the high plateaus of Central Africa. In China, the reports of Vortisch, and of certain missionary doctors in South China and of Fischer indicate that gastric ulcer is very rare in that country. On the other hand Oppenheim in 100 autopsies in Hongkong found gastric ulcers 11 times. In Central America, in one year there were 31 cases of ulcer of the stomach and duodenum and in Manila 86.

Other reports show that this condition may or may not be common. The reason for its prevalence in some areas is not clear but some of the evidence presented suggests that it does not apparently depend upon the grade of gastric acidity, although dietetic causes have been suggested. A simple carbohydrate diet does not predispose to it.

Carcinoma of the Stomach.—Malignant growths of the stomach and other parts of the alimentary tract, except in the cases of rectal bilharziasis, p. 1410, are rare in natives. DeLangen, who has made a special study of the subject, emphasizes its rarity in the Javanese. Reports from India and from Central Africa also indicate it is rare. On the other hand, the prevalence of primary carcinoma of the liver is emphasized in both the East Indies and among the negroes in parts of Africa.

Allergic Diseases.—The importance of food allergy in the diagnosis of clinical manifestations should be recognized. Beside the reaction from certain foods, there are many other causes, such as pollens, animal emanations, including feathers and hairs, smoke and dust, bacteria, especially of the respiratory group, and response to the injection of foreign proteins, whether sera for therapeutic use, or by inoculation by biting arthropods.

There also seem to be contributory factors, such as dysfunction of the endocrine glands, emotional states, heat, light and cold. The symptoms of allergy, or idiosyncrasy, as it is often termed, extend from a fatal shock, ushered in with severe pain of head and back, rapidly falling blood pressure and collapse, to mild attacks of erythema, urticaria or asthma. Nasal, pharyngeal, laryngeal and gastrointestinal symptoms also may be noted, as well as arthritic attacks, angioneurotic oedema and eosinophilia.

The influence of heat and light is often more intense in the tropics than in temperate climates, especially that of light, and the photo-dynamic qualities of many fluorescent substances may be very toxic or tend to produce alteration in enzyme action under the influence of sunlight. Allergic disturbances have been more commonly observed among Europeans residing in tropical countries than in natives. One of the best known of the allergic states is that associated with serum-sickness, where after about 8 days, as a minimum, following the injection of a therapeutic serum, there may be the development of fever, urticaria, hypotension and tenderness and stiffness of the joints. Stitt suggests that the early symptoms of Japanese bilharziasis may be of this nature, see p. 1680.

Anaemia as a clinical feature is observed almost everywhere in tropical countries. In addition to the anaemia which is so prevalent in the tropics from severe malaria and ancylostomiasis and which also occurs in *Bartonella* infection and sometimes in association with *Diphyllobothrium latum* and in the deficiency disease sprue, practically all other forms of anaemia which have been described in temperate climates may be encountered. The forms of anaemia resulting from specific conditions have been discussed generally under each disease. However on account of the special importance of the subject in the tropics a brief statement regarding the classification and different forms of anaemia is here deemed advisable.

Classification.—Stitt, Clough and Clough (1938) have pointed out that there is no single scheme of *classification* of the anaemias which is comprehensive and satisfactory. The most logical method is based on the *pathogenesis* of the anaemia. (1) Those due to loss of blood, the posthaemorrhagic anaemias. (2) Those due to inadequate blood formation, the deficiency anaemias and the aplastic anaemias. (3) Those due to increased blood destruction, the haemolytic anaemias. There are practical difficulties in the application of this classification, because in many cases inadequate blood formation and increased blood destruction both play an important role. Nevertheless this method has been utilized as far as practicable in the following discussion.

From the *morphological* standpoint the anaemias may be classified according to the mean corpuscular haemoglobin or color index as hyperchromic, normochromic, or hypochromic; and according to the mean corpuscular volume or volume index as macrocytic (megalocytic), normocytic, or microcytic. This classification has practical significance, since, in general, macrocytic anaemias are benefited by liver or liver extract, whereas the hypochromic anaemias are helped by iron. The terms, however, should be regarded as descriptive, and not as diagnostic. The terms "normocytic" and "normochromic" should be understood to mean merely that the *average* volume or haemoglobin content of the red cells is within normal limits. Otherwise they may be misleading, since the cells may be abnormal in other respects, and individual cells may be markedly abnormal in size and color.

The current tendency is to drop the use of the old terms "primary anaemia," supposedly due to some inherent disease of the blood-forming tissues; and "secondary anaemia," due to some obvious extraneous cause.

The following classification and description of the Anaemias, with very few additions, is given by Stitt, Clough and Clough.

A. Anaemias Due to Loss of Blood

These anaemias are hypochromic and usually microcytic.

1. **Acute Posthaemorrhagic Anaemia.**—The danger to life from a single profuse haemorrhage is from circulatory failure (shock) due to the lack of a sufficient volume of blood to fill the vessels, and not from a deficiency of haemoglobin. The first step in regeneration after an acute haemorrhage is the restoration of plasma volume, by the passage of tissue fluids into the vessels. This results in a dilution of the blood, with a gradual fall in red cell count and haemoglobin, which is not complete until from 24 hours to 3 or 4 days after bleeding has ceased. The resulting anaemia stimulates a rapid production and outpouring of new red cells which at first are normal reticulocytes. After a few days, however, the new cells tend to be imperfectly formed, to be inadequately supplied with haemoglobin, and to be hurried into the circulation before development (maturation) is complete. Reticulocytes are increased, polychromatophilic cells appear, and occasionally a few normoblasts. There is usually a neutrophilic leucocytosis and an increase in platelets. Many of the new red cells are smaller than normal and are pale. The color index and volume index fall. With the influx of new cells there is a gradual rise in the red cell count and (more gradual) in haemoglobin. The maximum abnormalities in the cells, however, are not reached until about the eighth or tenth day. In otherwise normal individuals completely normal conditions are restored usually after about 30 to 60 days.

2. **Chronic Posthaemorrhagic Anaemia.**—The changes in the blood are usually similar to those described above, but they tend to become more marked. In severe cases there is a marked degree of anisocytosis, a majority of the red cells are smaller than normal in diameter and volume, microcytes are numerous, and some poikilocytes may be present. As the iron stores of the body become depleted the concentration of haemoglobin in the cells diminishes, the color index and the saturation index fall, and the cells are pale. The centers may be colorless, so that the cells look like rings (pessary forms). There is no increase in the bilirubin in the serum. This is the typical picture of a *hypochromic microcytic anaemia.* The degree of anaemia may be severe. Counts of 2 million red cells and 20% of haemoglobin are not unusual, and rarely they may fall to half these figures.

The bone marrow is hyperplastic, and the predominant cells are normoblasts. The fatty marrow of the tibia and other long bones is often replaced by such red hyperplastic marrow.

While active formation of red cells continues, immature cells will be present. In cases with protracted bleeding, however, the marrow may become exhausted (aplastic). In such cases the immature red cells disappear, and there may be a reduction in the number of leukocytes and platelets. In exceptional cases of this type, particularly those with long continued small haemorrhages, the few cells which are formed may be more nearly normal, and the color index may approach 1.0.

Identical changes are met with in *hookworm infection.*

B. Anaemias Due to Inadequate Blood Formation

a. Anaemias Related to a Deficiency of Iron

These anaemias are hypochromic, and usually microcytic in type. They include: (1) Anaemias due to *lack of iron* in the diet, seen most frequently in infants and young children on a diet consisting largely or exclusively of milk. The anaemia appears earlier and is more severe in children of anaemic mothers, because of inadequate storage of iron in the foetal tissues.

(2) Anaemias due to *faulty absorption of iron* from the digestive tract, as in chronic diarrhoea, colitis, and some cases of sprue and indiopathic steatorrhoea.

(3) Anaemias due to *loss of iron* by external haemorrhage (already discussed).

(4) Anaemia in severe hookworm infection.

(5) Anaemia in some cases of cancer of the stomach.

(6) Anaemia in some cases after extensive operations on the stomach.

(7) Idiopathic hypochromic anaemia.

(8) Chlorosis.

Idiopathic hypochromic anaemia (primary microcytic anaemia, simple achlorhydric anaemia, chronic chlorosis) is a chronic disease largely (95%) limited to women, chiefly those between 20 and 50 years of age. Clinically it is characterized by an insidious onset, by the gradual development of marked weakness, lethargy, and nervous instability; and by digestive discomforts; gaseous distension, epigastric pain, occasionally diarrhoea and anorexia, or a fickle appetite. This often leads the patients to avoid meats, fruits, and green vegetables, foods rich in iron, and tends to aggravate the anaemia. Marked loss of weight is exceptional.

Soreness of the tongue and mouth is common. There is a *glossitis* and stomatitis which leads to atrophy of the mucous membrane. In at least half the cases there is atrophy of the papillae about the tip and margins of the tongue. The process often extends to the dorsum of the tongue, which becomes smooth and polished in appearance; and to the lips, which may show cracks and fissures about the corners of the mouth. In a small group of cases (*Plummer-Vinson syndrome, anaemia with dysphagia*) it extends into the pharynx and hypopharynx, causing dysphagia, which is attributed to reflex spasm of the inferior constrictor.

In about half the cases the nails become tender, thin, and brittle, they tend to loosen from the nail bed, and may become flattened or even concave and spoon shaped on the dorsal surface (*koilonychia*).

Paraesthesias of the extremities are common, as in pernicious anaemia, but combined sclerosis of the cord does not occur.

Menorrhagia is a common symptom, and the anaemia may erroneously be attributed simply to the loss of blood. Otherwise there is rarely any abnormal tendency to bleed, or any disturbance of coagulation. Fertility is but little affected.

The *spleen* is enlarged in about 40% of the cases.

The *skin* becomes inelastic and wrinkled, it may be waxy white or show slight brownish pigmentation. The sclerae are bluish white. There is never jaundice.

The *gastric juice* shows a hypochlorhydria or an achlorhydria in at least 85% of the cases, and a complete achlorhydria after histamine in

about 60%. Mucus is abundant. The ordinary ferments are often diminished or absent, but the intrinsic factor of Castle is retained.

The *blood* shows all the features characteristic of a hypochromic microcytic anaemia, as described in posthaemorrhagic anaemia. In the average patient the red cell count is between 3.5 and 4.0 million, the haemoglobin 6 to 8 Gm, or 40 to 50%. In severe cases, they may fall to 1.5 million and 2.0 Gm. The striking feature is the extreme pallor of the cells, and the degree of reduction in the color index (0.3) and in the mean haemoglobin content ($11\gamma\gamma$) and haemoglobin concentration (22%) in the red cells which may develop. The leukocytes and platelets are usually normal.

In untreated cases reticulocytes are sparse. However, biopsy shows the bone marrow to be markedly hyperplastic (normoblastic). There appears to be some obstacle to the maturation of the cells. An effective stimulus to their maturation and delivery into the circulation is provided by the administration (by mouth) of large doses of iron (6 Gm. or more per day of ferri et ammonii citras, or correspondingly large doses, in terms of their metallic iron content, of other preparations). In severe cases within 3 or 4 days after an adequate dose of iron is started, there is a *rise in reticulocytes* which reaches a peak on the seventh or eighth day, and which is roughly inversely proportional to the haemoglobin percentage. A satisfactory response is indicated by a rise in reticulocytes to 15% if the Hb. is 20%; to 8%, if the Hb is 40%; and to 5%, if the Hb. is 60%; and by an average daily rise in Hb. of at least 1% (in some cases 2%). An equally striking rise may be obtained in severe hypochromic anaemia of other types, as in hookworm anaemia (Castle and Rhodes, 1932), and even (temporarily) in cancer of the stomach. There is prompt relief (not always complete) of the symptoms and subsidence of the physical signs, except that the lingual atrophy and the achlorhydria persist. Liver extracts are ineffective.

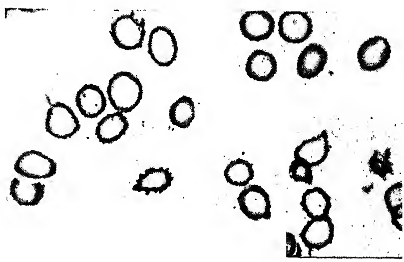

FIG. 391.—Red blood corpuscles showing deficient haemoglobin (achromia). From a well marked case of chlorosis. Wright's stain (×750.) (J. C. Todd, "Clinical Diagnosis.")

The disease is rarely directly fatal, even if untreated, but it often causes a protracted and profound degree of chronic invalidism. There is little tendency to spontaneous remission, until after the menopause. An exacerbation may be precipitated by a pregnancy, or by intercurrent infections.

The *etiology* is still obscure. A major factor is deficient iron absorption resulting from the defective gastric secretion. In some cases the latter is attributable to an inherent constitutional (sometimes familial) defect. In some it may be due to a chronic gastritis. A severe anaemia of any type, however, may cause a temporary disappearance of free HCl from the gastric juice. An identical condition has been described in patients (male as well as female) after gastroenterostomy, and after extensive gastric resection, and in some cases of cancer of the stomach. Other contributing causes are an

inadequate, ill-balanced diet, and the drain on the iron reserves resulting from menstruation and pregnancy. The defect is permanent, since *relapse* occurs if the administration of iron is stopped.

The great significance of chronic *occult bleeding* has been emphasized recently, notably by Heath. It may be that the syndrome is merely a type of chronic post-haemorrhagic anaemia complicated by inadequate absorption of iron and perhaps by other dietary deficiencies.

Clinically this disease resembles pernicious anaemia in many ways, although the changes in the blood are entirely different. They are similar in that both apparently depend on (different) deficiencies of gastric secretion, and both occasionally are familial. In several families idiopathic hypochromic anaemia has developed in females and pernicious anaemia in males, and rarely both diseases have developed successively in the same individual. The possibility of a double deficiency must be remembered, although outspoken examples of this are surprisingly rare.

Chlorosis is described as a disease of unknown etiology, limited to females and occurring chiefly during adolescence, characterized by the development of an anaemia of the hypochromic type, and by a prompt response to iron medication. The blood changes are identical with those in idiopathic hypochromic anaemia. The chief clinical differences are: (1) the younger age incidence in chlorosis, which usually subsides spontaneously at the age at which idiopathic hypochromic anaemia is most frequent; (2) normal or excessive amounts of HCl in the gastric juice in chlorosis, and (3) the response to smaller doses of iron. It is probable that chlorosis is due simply to an extreme lack of iron in the diet. Chlorosis has become rare in all countries and has practically disappeared in the United States.

Copper.—In animals (cattle, rats, swine) a diet made grossly deficient in copper as well as in iron produces an anaemia which does not respond to the administration of iron alone, but which improves promptly if copper is also given. A minute amount of copper is apparently necessary for the utilization of iron. It is very doubtful, however, whether a significant deficiency in copper occurs naturally in man, even on poor diets, except possibly in young children.

b. Anaemias Related to a Deficiency of the Anti-anaemic Factor in Liver

These anaemias are macrocytic, and usually hyperchromic in type. They include: (1) Primary pernicious anaemia (by far the most frequent and important).

Some cases of: (2) Sprue, idiopathic steatorrhoea, and other chronic intestinal disturbances. (Fistulae, multiple anastomoses, chronic obstruction).

(3) *Diphyllobothrium latum* (fish tapeworm) infection.
(4) Cancer of the stomach (rare).
(5) Complete resection of the stomach.
(6) Chronic diseases of the liver.
(7) Pregnancy (rarely).
(8) Tropical megalocytic anaemia.

Recent work by Minot, Castle, and many others has shown that the normal development and maturation of red cells is dependent on the activity of a specific substance which is commonly called the *anti-anaemic principle of liver*, or erythrocytic maturing factor. The production of this anti-anaemic principle depends on the interaction of two other substances: (1) An *extrinsic factor* which is furnished by the diet, is abundant in muscle and in yeast, rice polishings, eggs, milk and liver. It is not identical with any of the recognized fractions of the vitamin B_2 complex; and (2) an

intrinsic factor, which is present in normal gastric juice (possibly secreted also in the proximal part of the duodenum), and presumably is a ferment, although it is not identical with any of the previously recognized gastric ferments. The effective utilization of this anti-anaemic principle depends also (3) on adequate absorption from the gastrointestinal tract, and probably (4) on its storage by the liver, and presumably on its orderly release by the liver and distribution to the haemopoietic tissues as it is needed. A disturbance of any one of these functions, whatever the cause, tends to produce an anaemia which is macrocytic and hyperchromic in type. A macrocytic anaemia may occur, however, in diseases which are not associated with a disturbance of the anti-pernicious anaemia principle (leukaemia, primary aplastic anaemia, etc.).

In pernicious anaemia the disturbance is due to a partial or complete lack of the intrinsic factor in the gastric juice. In sprue and allied conditions deficient absorption is probably the usual cause. In chronic liver disease impaired capacity to store the material may be at fault. In some cases, as in certain tropical anaemias, there may be a lack of the extrinsic factor in the diet. In pregnancy there is probably an increased demand together with a relatively inadequate formation of the substance. Any of these anaemias is usually relieved by supplying adequate quantities of the active material, preformed, as by feeding liver, or by injecting parenterally suitable extracts of liver. Various British investigators have emphasized the fact that the administration of marmite (an autolyzed extract of brewers' yeast) is as effective as liver in those cases in which the anaemia is due to lack of the extrinsic factor, in many cases of sprue and idiopathic steatorrhoea, and to a limited extent in some cases of pernicious anaemia.

The active principle as it is obtained from liver differs in its thermostability and in other properties from that present within the gastrointestinal tract ("addisin," "haemopoietin"), and in the stomach tissue ("ventriculin"). Where this elaboration occurs is not known. That the liver serves as a storehouse for the substance seems certain. It has been demonstrated in the liver of patients dying of unrelated diseases by injecting suitable extracts of such livers (autopsy material) into patients with pernicious anaemia and observing a reticulocyte crisis, but it is absent in the liver of patients dying of untreated pernicious anaemia. It also disappears from the otherwise normal livers of gastrectomized swine, and of swine in which sprue has been experimentally produced.

Although the changes in the blood are usually more characteristic and more marked in degree in untreated cases of pernicious anaemia than in the other conditions mentioned, in some cases of the latter (e.g. sprue, fish tapeworm infection) they may be indistinguishable. In all these conditions the bone marrow shows megaloblastic hyperplasia in varying degree.

Pernicious anaemia is characterized clinically by an insidious onset, usually in adults of middle age; by the gradual development of a severe anaemia, with weakness, dyspnoea, and other symptoms of haemoglobin deficiency, by a protracted course, marked by remissions and exacerbations; and (in untreated cases) by a fatal termination.

During the active periods of the disease *digestive disturbances* are common: anorexia, gaseous distension, epigastric discomfort, sometimes nausea and vomiting, or diarrhoea, and occasionally crises of sharp colicky abdominal pain. Sore mouth and sore tongue due to a stomatitis and *glossitis* are common complaints. There is nearly always *atrophy of the papillae of the tongue*, which presents an abnormally clean, smooth, polished appearance. In the active stages there is fever, associated with evidences of increased blood destruction.

Paraesthesias of the extremities nearly always develop, and are often an early symptom. Focal degenerations of the cord (*combined sclerosis*) are common. They occur (1) in the posterior columns, causing *ataxia*, weakness, and minor sensory disturbances, particularly *loss of the vibratory sense* over the lower legs, diminished reflexes, occasionally hyperaesthesias; (2) in the lateral columns, causing *spasticity*, exaggerated reflexes, and less often sphincter disturbances. These changes are not proportional to the anaemia, and may antedate it. Rarely combined sclerosis occurs in patients who do not develop an anaemia, although as in typical pernicious anaemia they show an achlorhydria, and usually some degree of macrocytosis. Combined sclerosis is extremely rare in the other related anaemias. Peripheral neuritis also occurs, and may account for the paraesthesias in some cases. Minor cerebral disturbances are common.

In practically all cases there is an *achlorhydria*, even after histamine injection. The volume secreted is scanty and is increased but little by histamine. Mucus is scanty. The ordinary ferments are usually diminished, and often absent (true achylia). The gastric deficiency is permanent, even in well treated patients. A few rare cases have been reported, who showed free HCl in the gastric juice. The intrinsic factor has been absent in those cases of this group which have been tested as to this point. There is some evidence to indicate that the lack of intrinsic factor in pernicious anaemia, in some cases at least, is relative rather than absolute. It has been suggested, without as yet definite proof, that variations in the amount of intrinsic factor secreted may account for the fluctuations in the course of the disease.

The *blood* shows a marked reduction in the red cell count, frequently to 2.0, rarely to 0.5 million or less. The haemoglobin is relatively less reduced, so that the color index and mean haemoglobin content of the cells is increased. The volume index and mean corpuscular volume are also increased, more regularly and often more markedly than is the color index. The haemoglobin concentration in the cells is normal or slightly reduced. Anisocytosis is marked, and in severe cases it becomes more pronounced than in any other anaemia. Poikilocytes, microcytes, and macrocytes are numerous. Large, oval, deeply staining cells are highly characteristic, and a few are usually present in the early stages of the disease and during the remissions. The mean diameter is increased (to 8.5 to 9μ), and the cells are dark (the thickness is also increased).

A few *normoblasts* are present in most of the cases with marked anaemia. Typical *megaloblasts* are present at some stage of the disease in untreated patients, but they may be hard to find. They can rarely be found after treatment with liver, even though this is inadequate in quantity. During the *blood crises* which occasionally occur in untreated patients, there is a sudden outpouring of normoblasts and megaloblasts, reticulocytes, polychromatophilic cells, and cells with nuclear particles.

The platelets are reduced. There is a leukopenia. A few myelocytes are often present, but on the other hand there is a "shift to the right" in the sense of Arneth, with occasional huge neutrophiles containing hypersegmented nuclei with 6 to 10 lobes, "pernicious anaemia neutrophiles."

During the exacerbations of the disease there is mild jaundice, an increase in the bilirubin in the serum, and all the other characteristic

features of a haemolytic anaemia. It is generally believed, however, that this *increased blood destruction* is not a primary cause of the anaemia, but is the result of the entrance into the circulation of imperfectly formed cells which fall ready victims to the normal physiological processes for the removal of defective cells.

According to Minot, whose views are widely accepted, the fundamental disturbance in pernicious anaemia is inadequate cell formation. Although the marrow is hyperplastic, the megaloblasts are unable to complete their development and produce erythrocytes. There is an *arrest of maturation*, which is relieved by the administration of the active principle of liver.

This view has been questioned, however, notably by Dobriner and Rhoads (1938), who attempted to measure the rate of red cell formation and destruction in various stages of the disease. They utilized the rate of excretion of urobilin as a measure of red cell destruction, and that of coproporphyrin I as a measure of red cell formation. Although this substance is not directly concerned in the production of haemoglobin, they believe that it is a constant by product of the synthesis of coproporphyrin III, which is a constituent of haemoglobin, and that it can be used to measure the rate of formation of the latter. In pernicious anaemia during a relapse they found that cell (haemoglobin) production was actually accelerated as well as cell destruction. During a remission the rate of cell destruction fell to normal and cell formation was also somewhat reduced. They believe, therefore, that lack of erythrocyte maturing factor results in increased haemolysis rather than in a quantitative reduction in cell output.

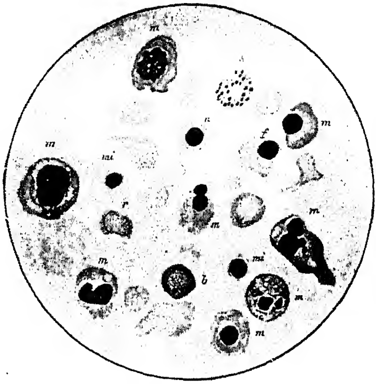

FIG. 392.—Pernicious anaemia. *M.m*, Megaloblasts; *n*, normoblast; *s*, stippling (punctuate basophilia). (Cabot.)

In patients with a red cell count below 3.5 million adequate liver therapy is followed by a transient *reticulocyte crisis*, which begins on about the third day, and reaches a peak on about the 7th or 8th day. The height of the peak varies inversely with that of the initial red cell count.

With a red cell count of 1.0 million the reticulocytes should reach 35 to 40%; with 2.0, about 20%; and with 3.0, about 5%. A lesser rise indicates either a mistaken diagnosis, inadequate dosage, or some complicating disease. If the initial dose of active principle has been too small, as indicated by an inadequate reticulocyte response, an increase in the dose will be followed by a second reticulocyte crisis. However, if the initial dose was adequate, a further increase will have no significant effect on the reticulocytes. These observations have proved to be of great practical value in the control of treatment. In favorable cases the red cell count may rise 2.0 million in one month, normal figures will be attained after 2 to 3 months, and the qualitative abnormalities entirely disappear except for the persistence of a few macrocytes. The

reappearance of these abnormalities or a fall in the red cell count indicates that the maintenance dose of liver is inadequate. Dried defatted stomach (by mouth) is as effective as liver so administered.

Failure to secure a satisfactory response is often due to deficient absorption from the gastrointestinal tract. In such cases excellent results can be obtained by *intramuscular injections*, which on the average are at least 50 times as effective as the administration of equivalent doses by mouth. With the best preparations a maximum response follows the daily intramuscular injection of extract from 15 to 20 Gm. of liver. A normal count can usually be maintained by a similar dose given once a week, and in some cases once a month. Patients with combined sclerosis require far larger doses, continued for many months. To control this process it may be necessary to give 2 or 3 times the amount which suffices to restore and maintain a normal red cell count. Improvement at best is slow, and is limited by the degree to which irremediable atrophy of nerve cells has occurred.

Although the pathogenesis of pernicious anaemia is now fairly clear, the underlying cause of the defective gastric secretion remains obscure. In some cases it is a familial constitutional defect. Many families have been reported in which two or more members have had pernicious anaemia, or in which other members have had achylia. Most patients with pernicious anaemia are sthenic in type, and have a light complexion, with fine, often prematurely grey hair. However, the disease may (rarely) occur in negroes.

The theory that a chronic *dietary deficiency* plays a part is attractive and receives some support from the experiments of Miller and Rhoads (1935). By feeding swine a suitably deficient diet, they produced a diseased state closely resembling tropical sprue and (less closely) pernicious anaemia in man. These animals showed an anaemia (usually macrocytic), with gastrointestinal disturbances and stomatitis, the intrinsic factor disappeared from the gastric juice and the anti-anaemic principle from the liver, and the bone marrow showed megaloblastic hyperplasia. The condition responded to injections of liver extract.

Pernicious anaemia appears to be very unevenly distributed in different parts of the world, according to the published reports. DeLangen and Lichtenstein (1936), in their studies upon the anaemias of the tropics state that during 20 years "we have never seen a case of pernicious anaemia in a native patient in Java, although in our Department for Internal Diseases in the Central Hospital in Batavia with its 300 beds a very intensive search for this blood disease has been made. Nor have we ever seen a case amongst the poor Chinese patients in Batavia, but on the other hand amongst the Europeans and the better situated Chinese in the tropics it is met with occasionally. In Africa no pernicious anaemia is found amongst the negro races; it is only found in certain of the tribes in the neighborhood of Lake Tanganyika whose food consists for the most part of meat and dairy products. This is of great interest for a study of the cause of pernicious anaemia. The countless cases of achylia gastrica found in the tropics appear not to contribute to the appearance of this serious disease if uncomplicated."

In Ceylon, the death rate is given as amounting to 3 per hundred thousand of the population but in Japan even less, 0.6, whereas in the northern United States the mortality is given as 6.9 and in England as 8.9 per hundred thousand. The difficulties of making a correct diagnosis in natives, especially when infected severely with an intestinal parasite, is emphasized.

Nutritional macrocytic anaemia is more or less universal in those tropical countries where the population subsists on an unbalanced and

deficient protein diet. Nutritional anaemia is frequently associated with malaria and syphilis and with severe infection in ancylostomiasis. Fairley, Bromfield and Conde have reported a macrocytic haemolytic type which is prevalent in Macedonia and is accompanied by splenomegaly due to chronic malaria infection. In this type there is a primary nutritional deficiency with a haemolytic agent, the malaria parasite, superadded.

Tropical megalocytic anaemia is a disease described as occurring in the native population of west Africa, India, and China (Wills and Mehta, 1930). It occurs chiefly in women between 20 and 30, and is often precipitated by pregnancy. The symptoms are those of any severe anaemia. Oedema is often marked. There may be a glossitis, but marked gastrointestinal disturbances are exceptional, and achlorhydria is rare. The blood shows a macrocytic hyperchromic anaemia which may be severe, with marked anisocytosis and many megalocytes, but without an increase in serum bilirubin, and but few poikilocytes and polychromatophilic cells. It is believed to be due purely to dietary deficiency (in extrinsic factor), as it is cured permanently by marmite. Wills recommended a daily dose of 30 grams of marmite. It is cured by oral or parenteral administration of the cruder types of liver extract, but not by highly concentrated extracts. (Wills and Evans, 1938.)

The anaemia also responds quickly to treatment with liver or liver extracts, although probably not to Anahaemin.

Differential Diagnosis.—The disease was originally confused with pernicious anaemia and it is indeed difficult to differentiate the two conditions by a simple blood examination; it has, however, a different age incidence.

In pernicious anaemia, there is achlorhydria and a positive indirect van den Bergh reaction, whilst in tropical nutritional anaemia the opposite is found. Glossitis is much more common in pernicious anaemia. Difficulty in diagnosis arises mainly in other tropical conditions, such as sprue, and indeed more than one anaemia-producing disease is often found in one and the same subject.

Tropical macrocytic anaemia, or the macrocytic anaemia of pregnancy, has for a long time been recognized in India, Malaya, West Africa and other tropical countries. Wills believed it could be differentiated from the pernicious anaemia of pregnancy which occurs in temperate climates. This anaemia of pregnancy is especially due to dietetic deficiencies aggravated by superadded infections of malaria and ancylostomiasis. DeLangen points out that what special diet leads to its production is not yet known. It appears, however, that the shortage of vitamins A and C play a part in the production, especially when at the same time the diet contains large quantities of fats. In women with a relative vitamin A and C shortage but with sufficient vitamin B, so long as they take but the smallest possible quantity of fat the disease practically is never seen. There appears to be no essential difference between this form of macrocytic anaemia of pregnancy and the tropical macrocytic anaemia described above and studied by Wills and Mehta and others.

Sprue is a tropical or subtropical disease of unknown etiology occurring most frequently in India, China, and the East Indies, where it is apt to attack white immigrants from temperature latitudes. It also occurs in the

West Indies and has been observed in the southern United States. It occurs chiefly in adults, more frequently in women. It is characterized by the gradual development of a chronic morning diarrhoea with progressive emaciation, weakness, and anaemia. The *stools* are typically bulky, greyish, pultaceous, and frothy, and contain large amounts of fat, chiefly as fatty acids. Glossitis and marked atrophy of the mucous membrane of the tongue and the entire gastrointestinal tract occur, associated with great flatulent distension. Free HCl is present in the gastric juice in most cases, and (if absent) may return during a remission. The intrinsic factor of Castle has been present in some cases and absent in others. There are no bone changes and no gross disturbance of calcium metabolism.

Anaemia is present in most cases, but varies much in severity (red cell count usually about 3.0, but may fall below 1.0). It is usually macrocytic and mildly hyperchromic in type, resembling pernicious anaemia except that the abnormalities are less marked. The anaemia often responds to yeast, and regularly to liver. It is probably due mainly to defective absorption of the anti-anaemic principle, or in some cases, to lack of the intrinsic factor. In a minority of the cases the anaemia is hypochromic, and these cases respond to iron but not liver (see also Chap. XXXI).

Idiopathic steatorrhoea (coeliac disease, non-tropical sprue) is a disease of temperate climates which usually begins in infancy or childhood, although it may not be recognized until adult life. It is characterized (1) by chronic diarrhoea, with abdominal distension, and fatty but not frothy stools; (2) by a disturbance of metabolism associated with defective absorption of calcium salts and vitamin D, and characterized by osteoporosis, pains in the bones, bone deformities, and pathological fractures; and (3) by emaciation and anaemia, which are often severe. Achlorhydria is rare. Glossitis may occur, and some degree of atrophy of the lingual papillae is not uncommon. Faecal excretion of calcium is increased, the blood calcium is often low, and latent tetany is common. Lenticular opacities may occur, and occasionally cutaneous eruptions suggestive of pellagra.

The anaemia is usually hypochromic in type, particularly in children. The color index is low, and anisocytosis is marked. The average cell diameter is usually within normal limits, but in some cases it is distinctly increased. Rarely numerous normoblasts have been present. The anaemia (but not the other symptoms) is relieved by iron, and it is attributed to defective absorption of iron.

In other cases, particularly in adults, the anaemia is macrocytic and mildly hyperchromic, resembling that commonly seen in sprue. In this type the anaemia responds to the administration of liver, or large doses of yeast preparations, and is attributed to defective absorption of the anti-anaemic principle.

Diphyllobothrium latum infection causes anaemia in only a very small proportion of the infected individuals. In these cases it may be severe and practically indistinguishable from pernicious anaemia, except that combined sclerosis rarely if ever occurs. The anaemia is usually cured permanently simply by expulsion of the worm. It is also cured by liver, but this must be continued until the worm is expelled. Free HCl is usually absent, but may return after expulsion of the worm. Hernberg (1936) reported finding the intrinsic factor.

Cancer of the stomach often causes anaemia, which is almost invariably hypochromic and microcytic in type. In the absence of bleeding it is usually moderate in degree, but may be extreme (R.B.C. 1.0, Hb. 15%), and quite like that in idiopathic hypochromic anaemia. In rare instances,

which are of theoretical interest but little practical importance, a macrocytic hyperchromic anaemia develops which may be indistinguishable from pernicious anaemia. This may temporarily improve under liver, and is attributed to loss of the intrinsic factor. The anaemia which follows extensive operations on the stomach also is more often hypochromic than hyperchromic in type.

Myxoedema frequently causes an anaemia which may be either hypochromic or hyperchromic in type. The latter type of anaemia is relieved by liver, and is attributed to a lack of intrinsic factor, which may be temporary (relieved by administration of thyroid alone), or permanent (requiring continuous administration of liver, which controls the anaemia, but not the myxoedema).

Pregnancy is so frequently associated with a mild hypochromic type of anaemia that some have regarded this as physiological. This usually increases gradually from the third to the seventh month, after which there may be some spontaneous improvement. The red cell count not infrequently falls to 3.5, and the Hb. to 50 to 60%. Occasionally much lower figures are observed. The anaemia responds well to iron, and is due to an iron deficiency. The latter is probably due in part, at least, to poor absorption, associated with the hypochlorhydria or achlorhydria which is commonly observed during pregnancy. It is partly the result of an increased need for iron to supply the foetal tissues. The apparent degree of the anaemia is somewhat exaggerated by the hydraemia which is present. The anaemia usually subsides after delivery. Failure to do so suggests the presence of idiopathic hypochromic anaemia, which is markedly aggravated by pregnancy. There is apt to be a recurrence in subsequent pregnancies.

In relatively rare instances a hyperchromic macrocytic anaemia develops. The changes in the blood resemble closely those in pernicious anaemia. There are evidences of increased blood destruction. The disease is severe, runs a relatively acute course, without remissions, and is often fatal if untreated. It may appear during the puerperium, but spontaneous recovery may occur after delivery. It responds well to liver (frequently also to transfusions), and recovery is usually permanent. It may not recur during subsequent pregnancies. There is usually free HCl in the gastric juice, but subacidity is common. Lack of the intrinsic factor—presumably temporary—has been reported in a number of cases. Strauss reported two cases who developed pernicious anaemia later.

c. Anaemias Related to a Functional Insufficiency of the Bone Marrow (the Aplastic or Aregeneratory Anaemias)

The inadequacy is usually relative, but in rare instances there appears to be a virtual cessation of red cell formation. The marrow as a rule is aplastic to a greater or lesser degree. In some cases, however, it shows marked hyperplasia, and there appears to be an arrest in the maturation of the cells. Among the more important conditions in which anaemia of this type occasionally occurs are the following:

1. In new born infants as a rare constitutional defect.

2. As a terminal phenomenon in anaemias of other types, as in chronic posthaemorrhagic anaemia, pernicious anaemia, and the myelophthisic anaemias.

3. Anaemias secondary to infection, particularly to such chronic infections as subacute bacterial endocarditis, chronic infectious arthritis, chronic pyogenic infections, and oral sepsis.

4. In advanced chronic nephritis (usually normochromic in type).

5. Malignant disease, in most of those cases in which haemorrhage does not play a part.

6. Dietary insufficiencies, other than simple lack of iron, including the avitaminoses, such as scurvy, etc.

7. Chronic poisoning with such chemicals as benzol, trinitrotoluol, arsenic, gold or radium salts (Martland, 1931).

8. After excessive exposure to X-rays or radium.

9. Acute idiopathic aplastic anaemia.

10. The myelophthisic anaemias.

This list manifestly includes many heterogeneous unrelated conditions, and the changes in the blood which they show vary in detail. A high grade of anaemia may occur in all of them. In the milder cases some new cell formation persists, and the blood shows imperfectly formed cells and immature red cells in small numbers. The blood often resembles that in cases of posthaemorrhagic anaemia, except that the hypochromia and microcytosis are usually less marked. In severe advanced cases the appearance of the blood is more distinctive. Despite a marked degree of anaemia, the individual red cells which remain are relatively normal. Anisocytosis is slight, and the color index and volume index are usually within normal limits. The anaemia is "normocytic" and "normochromic." Reticulocytes and other immature red cells are entirely absent. There is a neutrophilic leukopenia and a reduction in platelets which may be extreme, and associated with a (symptomatic) purpura haemorrhagica. There is no evidence of increased blood destruction.

In **Idiopathic aplastic anaemia** these features are seen in maximum degree. This is a rare disease of unknown cause, occurring chiefly in adolescents and young adults, characterized by progressive weakness and prostration, fever, rapidly developing anaemia, extreme leukopenia, thrombocytopenia, purpura and bleeding, and a fatal outcome within a few weeks or months. It is the "aleukia" of German writers. The spleen is not enlarged. The gastric juice is normal. The bone marrow in typical cases is markedly aplastic. Cases which are clinically indistinguishable, however, have shown marrow which is normally cellular or even hyperplastic, and in some of them reticulocytes, normoblasts, myelocytes and myeloblasts have appeared in the circulating blood. Krumbhaar has suggested the term pseudoaplastic anaemia or progressive hypocythaemia for such cases. The disease has been confused with pernicious anaemia, and (more reasonably) with idiopathic purpura and acute leucopenic leukaemia. Cases of severe poisoning with benzol, radium, etc., may present an identical picture.

Scurvy may cause a severe anaemia (R.B.C. 2.0, Hb. 30%) which is hypochromic and usually microcytic in type. It can not be explained by the (relatively trivial) haemorrhages which occur. It is not influenced by iron or liver, but responds to vitamin C with a reticulocyte crisis and rapid improvement.

Myelophthisic anaemia is a term applied to those conditions in which the erythropoietic tissue of the marrow is invaded and more or less crowded out by other tissue. Except in extensive leukaemic infiltration, the bulk of the invading tissue is rarely sufficient quantitatively to explain the anaemia on the basis of simple mechanical displacement, and a functional inadequacy of the remaining marrow must be assumed. These include:

1. Osteosclerotic anaemia.
2. The leukaemias.
3. Some cases of Gaucher's disease, and allied conditions.
4. Metastatic tumors in the bone marrow (frequently).
5. Multiple myelomata (occasionally).
6. Hodgkin's disease (rarely, disputed).

In many cases the anaemia is slight or moderate in degree, but it may be severe. Anisocytosis is often marked, but the color index and volume index are usually about normal or moderately reduced. In many (but not all) cases the blood shows changes suggesting intense stimulation (or irritation) of the marrow. There are numerous immature erythrocytes, including many normoblasts and macroblasts, and even megaloblasts. There is a neutrophilic leukocytosis, with myelocytes in varying number, and occasionally a few myeloblasts. They are sometimes classed as *erythroblastic anaemias*. (Vaughn). Areas of hyperplastic erythropoietic tissue are commonly found in the long bones, or sometimes in the spleen and other extramedullary tissues.

Osteosclerotic anaemia is a term usually applied to the condition described by Albers-Schönberg as "marble bone" disease. This is a rare disease of unknown etiology, which may be dependent on a constitutional abnormality of bone development, and is sometimes familial. It begins in early life, although it may not be recognized until the third decade. It is characterized by a peculiar type of irregular thickening of the bones, involving especially the shafts of the long bones. The new bone encroaches on and eventually may largely obliterate the marrow, which shows in addition extensive fibrosis. In spite of the thickening, the bones are fragile, and gross deformities and pathological fractures are common. In the later stages a severe anaemia develops (as low as R.B.C. 0.82, Hb. 10%, Vaughn), characterized by a marked erythroblastosis. The spleen and liver are much enlarged as a result of myeloid hyperplasia.

Myelosclerosis is a term applied by Mozer (1927) to a somewhat similar condition developing in adults, in which the bones become abnormally dense but not widened, and the cellular marrow is replaced by bone and fibrous tissue. Eventually a severe anaemia develops, with erythroblastosis and splenomegaly.

C. Anaemias Associated with Accelerated Blood Destruction (Haemolytic Anaemias)

Although accelerated blood destruction is a prominent feature of these diseases, in many of them inadequate blood formation is also important in the production of the anaemia. In some of them, as in pernicious anaemia, sickle cell anaemia, and probably haemolytic jaundice, the primary disturbance appears to be the formation of red cells which are inherently defective, and thus susceptible to the normal processes for removal of damaged cells. There is no positive evidence that anaemia is

produced by removal and destruction of normal cells, because of a pernicious overactivity of the reticuloendothelial tissues.

In nearly all cases red cells which are defective or which have been damaged are removed from the circulation before haemolysis occurs. If the rate of red cell destruction is accelerated (or if the liver is injured), the liver may fail to remove the bilirubin from the serum as fast as it is formed. As a result bilirubin accumulates in the plasma and gives the latter a yellow color. The icterus index rises, and the serum gives a positive (indirect) van den Bergh reaction. The skin and sclerae become more or less jaundiced. In some cases this may be deep, but usually it is relatively slight, and the color is a pale lemon-yellow rather than the orange tint of obstructive jaundice. The difference, however, is purely a quantitative one. The color in both cases is due to bilirubin. The urine becomes dark colored, and contains increased amounts of urobilin and urobilinogen, but no bilirubin (or only traces). The sediment may show renal epithelial cells containing haemosiderin granules. The urobilin in the faeces is increased. At autopsy the amount of iron in the liver and spleen is increased. These phenomena are marked only during periods of rapid blood destruction. If the latter is relatively slow, they will be slight, and perhaps limited to a small increase in the bilirubin in the serum.

The rapid destruction of red blood cells in the body, regardless of the disease in which it occurs, gives rise to a characteristic clinical syndrome. There is fever, sometimes a chill, weakness and prostration, pain in the back, and crises of acute colicky abdominal pain, with nausea, vomiting, and jaundice. It may simulate various acute abdominal conditions, and has led to unnecessary operations.

In rare instances in which a large number of red cells are rapidly destroyed, the cells may be haemolyzed in the circulation and the haemoglobin liberated into the plasma (*haemoglobinaemia*). If the amount of haemoglobin so liberated is large (when about 1/60 or more of the red cells are abruptly destroyed), *haemoglobinuria* occurs.

This is met with: (1) After transfusions of incompatible blood. (2) In paroxysmal haemoglobinuria. (3) In black-water fever. (4) Rarely in severe infections and intoxications of the types enumerated below (as in gas bacillus gangrene, and poisoning with arseniuretted hydrogen), and in favism. (5) In march haemoglobinuria. (6) In paroxysmal nocturnal haemoglobinuria.

A **haemolytic anaemia**, usually without haemoglobinaemia and haemoglobinuria, is met with chiefly in the following conditions:

1. Some acute infections, as gas bacillus gangrene, sepsis, especially puerperal sepsis and other streptococcal infections, typhoid fever, malaria, and Oroya fever. Rarely a profound anaemia may develop within a few hours.
2. Some cases of acute poisoning with certain drugs: phenol, benzol and their derivatives—nitrobenzene, trinitrotoluene, aniline, phenylhydrazine, acetanilid, and the sulphonamide drugs; saponin; potassium chlorate; lead and other heavy metals; arseniuretted hydrogen; snake venom; etc.
3. Rarely in leukaemia, Hodgkin's disease, carcinomatosis.
4. Extensive burns.
5. Idiopathic cases, including the acute febrile haemolytic anaemia of Lederer.
6. Favism.
7. Pernicious anaemia and related macrocytic anaemias during acute exacerbations of the disease.
8. Familial haemolytic jaundice.
9. Sickle cell anaemia.
10. Icterus gravis neonatorum.
11. Cooley's erythroblastic anaemia.

The morphological changes in the red cells in anaemias of this type are not distinctive, except in the specific diseases pernicious anaemia, haemolytic jaundice and sickle cell anaemia. In severe crises, spherocytes may be found. Anisocytosis and anisochromia are usually moderate and are typically less than in chronic posthaemorrhagic anaemia of the same degree. The volume index (mean corpuscular volume) and color index may be somewhat reduced, but more often they are within normal limits, and occasionally they are increased. These anaemias are not hypochromic, probably because the iron from the cells which have been destroyed is retained in the body and is readily available for the production of new haemoglobin. Evidences of active red cell formation, reticulocytes, polychromatophilic or stippled red cells, even normoblasts, are usually present and may be numerous, as in lead poisoning. In acute cases there is usually a leukocytosis and an increase in platelets. In protracted chronic cases the blood may finally assume the features of an aplastic type of anaemia.

Paroxysmal haemoglobinuria is characterized clinically by recurring brief paroxysms of chills, fever, pain in the back, prostration, cramps, vomiting or diarrhoea, numbness in the extremities, and haemoglobinuria. The individual attacks are usually precipitated by exposure to cold, or experimentally by holding the arm in ice water. They are followed by jaundice and (haemolytic) anaemia which may be severe. (R.B.C. 1.0.)

The haemolysis is brought about by an haemolysin of the usual complex type. The stable constituent ("amboceptor") is peculiar in that it will combine with cells only at a low temperature. Once combined, it renders the cells susceptible to the lytic action of complement when warmed to body temperature (the *Donath-Landsteiner phenomenon*).

No.	Serum, 0.5 cc.	Cell suspension 0.2 cc.	Complement, cc.	Salt sol., cc.	Positive result
1	Patient's	Patient's	0.2	0.1	Haemolysis
2	Control	Control	0.2	0.1	0
3	Patient's	Control	0.2	0.1	Haemolysis
4	Control	Patient's	0.2	0.1	0
5	....	Patient's	0.2	0.6	0
6	....	Control	0.2	0.6	0

The *haemolysin* can usually be demonstrated in the following simple manner. Put about 1 cc. of fresh (warm) blood in each of two test tubes and keep at body temperature until the serum has separated. Keep one tube in the water bath at 37°C. as a control and put the other in ice water for 5 to 7 minutes. Then put this in the water bath for an hour. If the serum in the control tube remains colorless, the presence of the haemolysin is indicated by more or less tingeing of the serum in the second tube. If the result is doubtful, add to each tube a little additional complement and return to the water bath. (Use 1 to 10 dilution of fresh guinea pig serum, or fresh normal human serum of the same blood group; this is usually necessary if the blood has been chilled for more than 10 minutes.)

For more precise demonstration withdraw about 10 cc. of blood from the patient in a warm syringe, allow about 8 cc. to clot (for serum) and oxalate the rest. The blood, solutions and apparatus must be kept at body temperature throughout all manipulations. Wash the cells and prepare a 5% suspension. Secure 10 cc. of normal human

blood of the same blood group and treat in the same way. Prepare a 1 to 10 dilution of fresh guinea pig serum as complement. Set up tubes as shown on page 361.

Put all tubes in ice water for 10 minutes and then in the water bath at 37°C. for half an hour. A positive reaction is indicated by haemolysis in tubes (1) and (3) and by absence of haemolysis in all the other tubes.

The condition is regarded as a rare late manifestation of *syphilis*, since a large proportion of patients give a positive Wassermann reaction, and it can sometimes be cured by adequate treatment of the syphilis. The haemolysin has been observed in some cases of late syphilis, who show no clinical symptoms of paroxysmal haemoglobinuria, but not in other conditions.

The disease must be differentiated from black water fever and other rare forms of haemoglobinuria. *March haemoglobinuria* may follow unusual muscular exertion, such as long marches or standing for hours in a lordotic posture.

Paroxysmal paralytic "haemoglobinuria" (similar to a relatively common disease of horses) has been reported in a few human cases. There are recurring attacks of extreme muscular weakness, followed by "haemoglobinuria," and later by more or less marked muscular atrophy but little or no anaemia. The pigment excreted is *myoglobin.* The muscles in fatal cases show marked degenerative changes and loss of pigment ("fish flesh"). A somewhat similar acute degeneration of striated muscle with myoglobinuria has been observed in Königsberg ("Haffkrankheit") in individuals (and in cats) who had eaten fish which had ingested poisonous resinous acids, the waste products of cellulose factories.

Paroxysmal nocturnal haemoglobinuria is a chronic relapsing disease of unknown etiology characterized by an insidious onset with weakness, anaemia, jaundice and later recurring attacks of haemoglobinuria without obvious exciting cause, which usually occur at night and lead to severe anaemia. The blood shows a continuous haemoglobinaemia, a leukopenia, many reticulocytes, and normal fragility. Ham (1939) reported that the increased haemolysis occurred during sleep and was associated with a fall in the pH of the plasma. The abnormality seemed to be not in the plasma but in the cells, since they were haemolyzed in acidified fresh serum, either of the patient or of normal individuals of the same blood group. Splenectomy has not been beneficial. (Reviewed by Witts (1936) and by Hamburger and Bernstein, 1936.)

In none of these conditions is there any relation to syphilis or to exposure to cold, and the Donath-Landsteiner phenomenon is absent.

Lederer's acute haemolytic anaemia is a syndrome observed chiefly in children and young adults, and characterized clinically by an acute onset with fever, by the rapid development of a severe haemolytic anaemia (R.B.C. to 1.0) with great prostration, jaundice, abdominal pain, vomiting, diarrhoea, often purpura and haemorrhages, occasionally anuria and uraemia. There is usually a leucocytosis and often many myelocytes and some myeloblasts appear in the blood. It is often fatal if not properly treated, but can usually be cured by prompt and repeated transfusions, or if these fail, by splenectomy. It can not be distinguished sharply from other clinical types of haemolytic anaemia of unknown cause, and is probably not a disease entity.

Lead poisoning frequently causes an anaemia which is usually hypochromic and moderate in degree (R.B.C. 3.0 to 4.0), but may become severe. In severe cases it may cause an acute haemolytic anaemia. DeLangen has reported its prevalence in natives in the Dutch East Indies both from accidental ingestion of lead and from the very extensive use of face powders with high lead content. Young children thus become poisoned from their mothers. The most characteristic feature of the blood is the appearance of many reticulocytes and stippled cells. These cells may appear within a few days after exposure to lead, in the absence of appreciable anaemia. Although stippled cells may appear in any anaemia in which active red cell regeneration is taking place and although they may be sparse in some

cases of lead poisoning, their early appearance and their presence in large numbers is highly characteristic.

Actual counts of *stippled cells* have been utilized to detect and measure the degree of absorption of lead in industrial workers. In Germany a count of from 100 to 300 per million red cells has been regarded as an indication for enforced change of occupation. Belknap (1935) has found that men with counts of 500 to 1000 per million might continue at work for years without clinical symptoms of lead poisoning, but that an abrupt increase above these figures was usually followed by acute symptoms. Counts of 40,000 per million, and more have been observed. The number may be estimated by counting the number of stippled cells in 50 oil immersion fields in an ordinary thin film, and multiplying this figure by 100 (the average number of red cells per field is about 200, and this should be roughly checked by those not experienced in such counts). McCord's basophilic aggregation test in which dried thick films without fixation are stained with Manson's methylene blue should be used if the cells are sparse.

An increase in *reticulocytes*, although less specific, is an earlier and more sensitive sign of lead absorption than the appearance of stippled cells. There is a rough parallelism between the counts of the two types of cells. Jones (1935) found the number of reticulocytes trebled with 100 stippled cells per million, and 5 times the normal with 1000 stippled cells per million. Reticulocyte counts of 16% and more have been observed in acute poisoning. Jones found appreciable numbers of normoblasts in about 5% of the chronic cases.

The resistance of the red cells to hypotonic salt solution is increased, but the cells appear to be abnormally fragile and susceptible to mechanical injury (Aub).

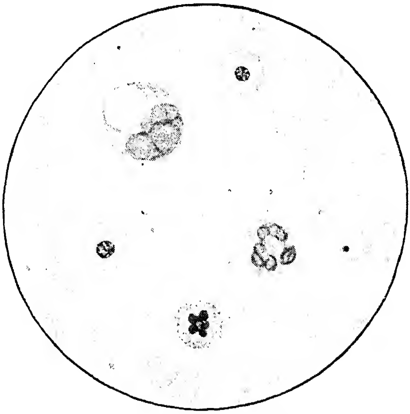

FIG. 393.—Sickle cell anaemia. Severe case showing an unusual number of sickled cells in a stained film. Three normoblasts. Upper left: Macrophage containing a red corpuscle.

Acetanilid and related drugs in overdose cause a transformation of haemoglobin to *methaemoglobin*. This imparts to the mucous membranes a characteristic, dusky, cyanotic tinge. It can be recognized by spectroscopic examination, but must be differentiated carefully from sulphaemoglobin which gives a closely similar spectrum. As a rule, after removal of the poison there is a reversion to normal haemoglobin, without much injury to the red cells. More rarely it causes a severe acute haemolytic anaemia, associated with a leukocytosis and occasionally an erythroblastosis.

Sickle cell anaemia is an hereditary constitutional anomaly practically limited to negroes, transmitted by either sex as a dominant Mendelian characteristic, and characterized by the tendency of the red cells (in sealed fresh preparations) to assume characteristic bizarre shapes. The cytoplasm of the cells at two or more points becomes drawn out into elongated spine-like projections, so that the cells become crescentic, or more often oat-shaped or irregularly stellate. Hahn and Gillespie found that the cells would resume the normal shape if oxygen was supplied to the preparation, and would again "sickle" if it was withdrawn. These dis-

tortions are not seen in ordinary fixed films, except to a slight extent in a few cells in the severest cases.

A majority of the individuals who show this trait are symptomless. In a few cases recurring attacks of acute haemolytic anaemia occur, with partial recovery in the intervals. In addition to the usual symptoms due to acute haemolysis, older patients often complain of deep seated pain in the bones and joints, often associated with osteoporosis in roentgenograms; and chronic punched-out ulcers over the lower legs. The skull may show changes similar to those in Cooley's anaemia. The spleen is often enlarged in young children, later it becomes small and fibrotic. Symptoms appear in childhood (if at all), and if severe, the prognosis is unfavorable. Retardation of development, both mental and physical, is common.

The degree of anaemia is variable, but it may be profound (R.B.C. 1.0 or less). The color index and volume index vary, but usually are about 1.0. There are many reticulocytes and polychromatophilic cells, and often many normoblasts. The fragility of the red cells is normal. There is usually a leukocytosis and an increase in platelets. In severe cases monocytes containing phagocyted red cells can often be found.

Elliptical red cells, which occur as a rare familial trait in Caucasians, must be sharply differentiated. The cells do not "sickle," and the condition does not cause anaemia or impair the health.

Haemolytic Jaundice.—Two types have been described: (1) a congenital familial form, and (2) an acquired form, occurring later in life, and without a familial history.

Familial haemolytic jaundice depends upon a constitutional anomaly which is transmitted by either sex as a dominant Mendelian characteristic. The disease usually becomes manifest during the second or third decade, and is characterized by recurring attacks ("crises") of haemolytic anaemia, with the usual symptoms of acute haemolysis and outspoken jaundice. The serum bilirubin may be increased to from 10 to 50 times the normal. In the intervals there is partial recovery, but some anaemia and jaundice persist. The acute attacks may be precipitated by an acute infection or other associated disease, but often no exciting factor can be found. Gall stones develop in about half the cases, and gall stone colic and obstructive jaundice may mask the underlying disease. The spleen is regularly enlarged. The bone marrow shows a marked hyperplasia which is usually normoblastic. The bones may show thickening and rarefaction in roentgenograms. Extra-medullary areas of hyperplasia may occur. The disease causes marked disability, but is rarely directly fatal.

The degree of *anaemia* is usually slight or moderate, but may be marked. The average red cell count is from 3.0 to 3.5. The color index and volume index (and mean corpuscular volume) are normal or slightly increased. The distinctive features are: (1) The diameter of the red cells is diminished but the mean volume is not significantly altered; hence the thickness must be increased, so that the cells are more globular than normal. Naegeli (1919) termed them "spherocytes," and regarded their formation as a manifestation of the constitutional anomaly underlying the disease. Krumbhaar has called the disease "spherocytic icterus." (2) The resistance to hypotonic salt solution is diminished. Haemolysis usually begins in concentrations from 0.5% to 0.6%, rarely even 0.8% (instead of 0.44%), and may be complete at 0.4% to 0.48% (instead

of 0.34%). Not infrequently, however, the divergence from normal is relatively slight. (3) Reticulocytes are much increased, often to 10% or 20%, rarely to 50% and more. Other evidences of regeneration are present, including frequently a few normoblasts.

Splenectomy stops the rapid cell destruction and usually effects a permanent clinical cure, although the abnormal shape and diminished resistence of the cells persist in some degree. Relapses have occurred, and in some cases have been associated with hyperplasia of accessory spleens.

Not infrequently examination of the relatives of a patient reveals *latent cases*, with a slightly diminished resistance of the red cells to hypotonic salt solution as the only manifestation of the anomaly.

Acquired haemolytic jaundice, as usually defined, differs fundamentally from the familial type only in the late onset and apparent lack of hereditary factors. The condition is usually attributed to some infection or other organic disease (which is not always demonstrable). Clinically the disease is described as usually more severe than the familial type, the anaemia more profound (R.B.C. average 2.0, minimum 0.5), and a fatal outcome common. Splenectomy is less regularly effective. The globular shape and diminished resistance of the red cells are often less clear cut. As these features constitute the only decisive characteristic by which the condition can be differentiated from ordinary acute haemolytic anaemias, many have questioned its existence as a distinct disease entity.

Dameshek (Medicine, 1940) has reported producing in animals, by injections of haemolytic serum, an anaemia which closely resembles acquired haemolytic jaundice in man, including the presence of spherocytosis and increased fragility of the red cells. He has pointed out the frequent occurrence of spherocytes in severe haemolytic anaemias in man of both known and unknown etiology, and believes no distinction can be drawn between acute haemolytic anaemia and acquired haemolytic jaundice. Spherocytosis would therefore not indicate a constitutional anomaly of the bone marrow, but would result from injury to the mature red cells in the circulation, presumably by some lytic substance in the plasma.

Congenital Erythroblastic Anaemia (Erythroblastosis Foetalis).—This is a congenital, familial (but not directly hereditary) disease of unknown etiology. It appears in three distinct clinical types which probably represent different stages, or different degrees of severity, of the same process (Diamond, Blackfan and Batty, 1933). Successive children in the same family are often affected, and may show different types of the disease. All have the following characteristics in common: (1) A severe hypochromic type of anaemia (R.B.C. often 1.0 or less). (2) Extraordinary numbers of circulating erythroblasts (up to 100,000 per cmm.) of every stage of maturity. (3) Extreme hyperplasia of erythropoietic tissue, both intramedullary and extramedullary, in the spleen, liver, and many other organs. (4) Great enlargement of the spleen and liver. (5) A leukocytosis with many immature cells. (6) Often a bright golden-yellow vernix caseosa and amniotic fluid.

a. Hydrops Foetalis.—In this type the infant is still-born or dies within a few hours. There is marked generalized oedema of the placenta and foetal tissues, cardiac dilatation, dyspnoea and cyanosis.

b. Icterus Gravis Neonatorum.—There is jaundice, which may be present at birth, or may appear during the first 12 to 48 hours. It increases rapidly to a deep orange-brown color. Petechiae may occur. The disease, if untreated, is fatal within the first week in about 80% of the cases but it can often be cured by repeated small transfusions, or (Hampson, 1929) by intramuscular injections of normal human serum. Recovery, if it occurs, is complete and permanent. The tissues are deeply icteric, including in some cases the basal ganglia ("Kernicterus"), and there are extensive deposits of iron pigment.

c. Congenital anaemia of the new born is practically identical with the preceding type except for a milder course and for the absence of jaundice. It is distinguishable from the simple hypochromic anaemias chiefly by the erythroblastosis and splenomegaly.

The erythroblastic anaemia of Cooley is a congenital and often familial constitutional anomaly largely limited to children of eastern Mediterranean races. It is characterized by (1) a hypochromic type of anaemia which becomes severe (R.B.C. 1.7, Hb. 10%); (2) mild jaundice, with hyperbilirubinaemia; (3) a leukocytosis; (4) a marked erythroblastosis (often 100 or more per 100 W.B.C.); (5) a marked generalized hyperplasia of erythropoietic tissue with enlargement of the liver and spleen; and (6) peculiar, characteristic changes in the bones, especially the skull. The cortex is thinned, and the medullary portion becomes greatly widened and porous, so that in roentgenograms the trabeculae stand out like fine sharp spines. The thickening of the bone is so great that it gives the patients a characteristic mongoloid physiognomy with high, bulging forehead and prominent malar eminences.

The anaemia is not noted at birth, but becomes evident within the first year or two. The disease runs a chronic, slowly progressive course and is usually fatal within the first ten years. However some mild cases in adults have been described. Splenectomy has proved useless, and is followed by a great increase in the erythroblastosis (up to 1500 nucleated red cells per 100 W.B.C.).

Miscellaneous Conditions

Banti's disease is a disease of unknown cause, occurring chiefly in young adults, and characterized by the gradual development of a hypochromic anaemia, associated with splenomegaly, progressive weakness and emaciation, a tendency to gastric haemorrhages, and a terminal atrophic cirrhosis of the liver, with ascites and jaundice. The anaemia is usually moderate (R.B.C. 3.0, Hb. 50%), but evidences of red cell regeneration are scanty. At times there are evidences of increased red cell destruction. The fragility of the red cells is normal. There is usually a neutrophilic leukopenia and a moderate reduction in platelets. Splenectomy in the early stages of the disease is usually curative, or at least temporarily beneficial. The advisability of this procedure has been questioned in cases with normal platelets because of the frequency of postoperative thrombocytosis and thrombosis in this group.

The cases commonly included under this heading constitute a heterogeneous group, and many investigators deny the existence of Banti's disease as a definite entity. Similar pathological changes may follow occlusion of the splenic or portal veins from various causes. The condition should be regarded as a clinical syndrome rather than as a distinct disease.

Anaemias in young children, regardless of their cause, often differ from those in adults in the type of cellular response. Immature red cells are more numerous, particularly normoblasts, macroblasts, and even megaloblasts. There is more regularly a leukocytosis (or lymphocytosis), which may be marked and accompanied by many immature leukocytes. There is often enlargement of the spleen, liver, and lymph glands, due to erythroblastic hyperplasia in these organs. The *anaemia pseudoleukaemica infantum* of Von Jacksch represents in marked degree such an infantile response to anaemia resulting from a variety of infectious diseases and metabolic or nutritional disturbances.

Polycythaemia

By a polycythaemia, or more precisely an *erythrocytosis*, is meant an increase above the normal in the number of red cells per cmm. of blood.

In a *relative polycythaemia* there is no increase in the total number of red cells in the body. It is seen chiefly as a transient phenomenon associated with dehydration, and is a rough measure of its severity. A local

erythrocytosis may occur as a result of local stasis, whether due to chilling and acrocyanosis, or to the use of a tourniquet.

In an *absolute polycythaemia* there is an increase in the blood volume as well as in the red cell count. There is a pathological increase in the total number of red cells in the body. This occurs (1) in the specific disease erythraemia (polycythaemia vera), and (2) as a compensatory response to anoxaemia in the following conditions (secondary polycythaemias):

1. *Normal Individuals at High Altitudes.*—Within an hour or two after a sudden ascent (as in aviation) there may be a rise of 500,000 red cells per cmm., due to an outpouring of cells from the spleen, which disappears promptly after descent to normal levels. With a sojourn at high altitudes, in some individuals there is an increased production of red cells, with a transient rise in reticulocytes, which is stimulated by the low O tension. The red cell count may reach 8 million or more. In rare instances typical erythraemia has ensued. In the higher altitudes in the Andes "sorroche" is common especially in European travellers. The prevailing symptoms are dizziness, headache, nausea, rapid pulse, tachycardia, increased respirations and high red blood cell count.

2. In chronic myocardial insufficiency with cyanosis, as in some cases of mitral stenosis and congenital pulmonary stenosis.

3. In emphysema, in diffuse pulmonary fibrosis from any cause, and in sclerosis of the pulmonary arteries (*Ayerza's disease*).

4. After mild chronic poisoning with a variety of blood poisons, such as lead, carbon monoxide, etc.

Erythraemia, or polycythaemia vera (rubra), is a chronic disease of unknown etiology, characterized by an erythrocytosis with an increase in total blood volume, by a peculiar intense flushing of the skin and mucous membranes, by enlargement of the spleen, and by a normoblastic hyperplasia of the erythropoietic tissues. It affects chiefly adults over 50 years of age. It is characterized clinically by an insidious onset and a protracted chronic course, with weakness, headaches, vertigo, tinnitus, paraesthesias, nervous irritability and mild mental disturbances. The skin, especially of the face and extremities, acquires an intense, mottled, brick-red color, the mucous membranes a deep purplish red or plum color, due to marked dilatation of the superficial capillaries together with slowing of the local circulation. Haemorrhages and thromboses are common. There is often hypertension, and resulting myocardial insufficiency. Occasionally cirrhosis of the liver develops, or arteriolosclerosis of the kidney and renal insufficiency. The basal metabolic rate is increased in about half the cases.

The blood at some stage of the disease usually shows a red cell count of 8 million or more, rarely even 12 to 15 million. However, the count is not invariably or constantly so high. In undoubted cases it may be between 5 and 6 million. The blood volume is always increased and may be double the normal, a decisive point in doubtful cases. The haemoglobin is increased to a relatively less degree; usually 19 to 24 Gm., 130% to 160%. The viscosity is from 2 to 5 times the normal. The individual red cells are somewhat small and pale, they show slight anisocytosis, and usually a moderate increase in reticulocytes and other immature forms. Platelets are increased. There is a moderate leukocytosis,

Splenomegaly in Diseases of the Blood. Differential Diagnosis

	Time of onset	Duration	Splenomegaly	Pathology of Spleen	Splenectomy beneficial	Haemorrhages	Anaemia	Leukocyte count
Pernicious anaemia	Adult late	Many years	Slight, occasional	Fibrosis	No	Rare	Severe	Low
Idiopathic hypochromic anaemia	20–50	Many years	Slight in 25–30 %	?	No	Rare	Moderate to severe	Normal or low
Familial haemolytic jaundice	Congenital or childhood	Life	++	Congestion pigmentation	Usually curative	Rare	Slight to severe	Variable
Acquired haemolytic jaundice	Adult	Many years	++	Congestion pigmentation	Often	Rare	Severe	Variable
Banti's disease	Childhood; young adult	Several years	+	Hyperplasia fibrosis	Often	Gastric common	Slight to severe	Low
von Jaksch anaemia	Infancy	Several months	++	Hyperplasia fibrosis	In some cases	Rare	Often severe	Increased
Idiopathic thrombopenic purpura	Variable often in childhood	Many years	Rare	None characteristic	Often curative	+++	Severe after bleeding	Variable often reduced
Anaphylactoid purpura	Childhood	Brief attacks	+ in some cases	None characteristic	No	Trivial	No	Increased
Polycythaemia	Adult late	Several years	+	Congestion hyperplasia	Probably harmful	Occasional	No	Increased
Chronic myeloid leukaemia	Adult	2–5 years	+++	Myelocytic infiltration	Harmful	Occasional	Becomes severe	Very high
Chronic lymphatic leukaemia	Adult	2–10 years	++	Lymphocytic infiltration	No	Rare	Becomes severe	Usually very high
Acute leukaemia (myelogenous, lymphatic, monocytic)	Childhood; youth	A few months	+	Primitive cell infiltration	Harmful	Common ++	Severe	Low, normal or high
Hodgkin's disease	Any age	1–5 years	++	Peculair hyperplasia, fibrosis	No	No	Becomes severe	Variable
Lymphosarcoma	Any age	1–3 years	+ in some cases	Hyperplasia of lymphocytes	No	No	Slight to moderate	Usually normal
Gaucher's disease	Infancy	Life	+++	Hyperplasia of R.E. (foam) cells	No	Occasional	Slight	Normal or low

which may be marked and associated with a slight myelocytosis. Rarely in the terminal stages the blood may show an aplastic anaemia, or the presence of myeloblasts and many myelocytes may suggest a myeloid leukaemia.

Symptomatic relief with restoration of a normal blood count may follow radiation of the long bones, or more certainly the *cautious* administration of phenylhydrazin.

The resemblance of the symptoms and changes in the blood similar to those of mountain sickness has suggested that there is an anoxaemia of the tissues in erythraemia. However, no mechanism for the production of such an anoxaemia has yet been demonstrated, except that thickening of the walls of the capillaries has been described. Some regard the process as a malignant hyperplasia, analogous to leukaemia.

Leukopenia.—In kala-azar in which there is usually considerable anaemia the most remarkable change in the blood is the leukopenia. The leucocytes are frequently so reduced that instead of there being 1 white to about 650 red as in a normal person, the proportion is often 1:1500 to 1:2000. (See p. 268.)

Leukaemia.—Diseases involving primarily the leucocytes and characterized by an abnormal proliferation of the leukopoietic tissue, and by the appearance in the circulating blood of immature leucocytes with usually a marked increase in the number of circulating leucocytes, are apparently rare among the inhabitants of tropical countries. Manson-Bahr in his text book of Tropical Diseases (1940) does not refer to Leukaemia.

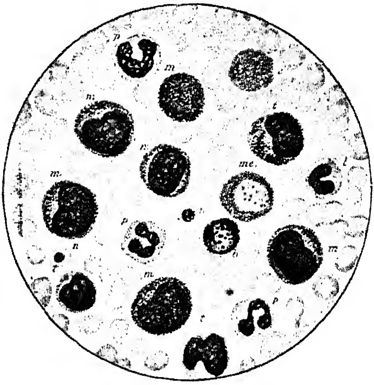

FIG. 394.—Chronic myelogenous leukaemia. *m*, Myelocyte; *p*, polymorphonuclear; *b*, mast cell; *n*, normoblast. (Cabot.)

Of the three types of leukaemia, occurring in temperate climates, termed myelogenous, lymphatic, or monocytic, depending upon which of the leukopoietic tissues is involved, apparently only the myelogenous has been reported in the tropics and this form rarely.

Chronic myelogenous leukaemia, the most common type, is a disease of adults, characterized clinically by an insidious onset, with symptoms referable to the enlarged spleen, and progressive weakness, emaciation, and anaemia. Symptoms of myocardial insufficiency and digestive disturbances frequently occur, and occasionally haemorrhages, pruritus, priapism, and pain and tenderness in the long bones. The spleen is huge, often reaching to the right anterior superior spine. The liver is usually much enlarged, the lymph glands rarely.

The *blood* shows a total leucocyte count which is usually between 100,000 and 500,000 per cmm., but rarely it may reach 1.0 or 1.5 million. Occasionally it is within the range of an ordinary leucocytosis. As a rule the bulk of the leucocytes are polymorphonuclear neutrophiles and neutrophilic metamyelocytes (30% to 65%) neutrophilic myelocytes are always present (5% to 70%, usually 20% to 50%). Eosinophiles

and basophiles are increased, and occasionally either type of cell may be markedly increased (up to 40%). The corresponding types of myelocytes are present, and there may be an occasional primitive myelocyte or myeloblast. Pathological leucocytes of bizarre appearance are often found. The lymphocytes and monocytes are relatively reduced.

DIFFERENTIATION OF THE ANAEMIAS BY THE BLOOD PICTURE

	Haemoglobin	Red cells	Color index	Volume index	Anisocytosis	Poikilocytosis	Macrocytes	Microcytes	Color of cells	Polychromatophilia	Reticulocytes	Nucleated red cells	Icterus index	Urobilinuria	Leukocyte count	Platelets	Gastric acidity	Response to iron	Response to liver	Splenomegaly
Acute posthaemorrhagic...	50–80	3.0–4.5	N-L	N-L	+	o	o	±	N-P	+	+	±	N	o	H	H	N	+	o	o
Chronic posthaemorrhagic.	20–60	2.0–4.0	L	L	$+^2$	+	±	+	P	+	+	±	L N	o	N H	N-H	N	+	o	o
Idiopathic hypochromic...	20–60	3.5–4.5	L	L	+	±	±	$+^2$	P	o	N	o	L	o	N-L	N	o	$+^2$	o	±
Hookworm..............	30–70	2.0–4.5	L	L	+	±	o	+	P	o	N-	o	N-L	o	V	N	V	+	o	o
Cancer of stomach........	20–80	2.0–4.5	L	L	+	±	o	+	P	±	V	o	N	o	N-H	N	o	+	o	o
Chlorosis..............	20–60	3.5–4.5	L	L	±	o	o	+	P	o	o	o	L	o	N	N	N	$+^2$	o	o
Chronic infection, severe..	30–70	2.5–4.5	L	L	+	o	o	+	P	o	o	o	N-L	o	V	N-L	N	o	o	±
Malaria..............	20–70	1.0–4.0	N	N	+	±	±	±	N	+	N-+	o	H	+	L	V	N	o	o	+
Pernicious, active stage...	30–70	1.0–3.0	H	H	$+^3$	+	$+^2$	+	D	+	+	+	H	+	L	L	o	o	$+^3$	±
Sprue: (1) macrocytic.....	30–70	2.0–3.5	H	H	$+^2$	+	$+^2$	+	D	±	N-	±	N	±	L	V	N-o	o	$+^2$	o
(2) hypochromic...	30–70	3.0–4.5	L	L	+	+	+	+	P	o	N	o	N	o	L	V	N	+	o	o
Aplastic..............	30–60	1.5–3.5	N	N	±	±	o	o	N	o	o	o	N	o	L	L	N	o	o	o
Erythroblastic..........	30–80	1.5–4.5	N-L	N	+	±	±	±	N	+	$+^2$	$+^3$	N	o	H	H	N	o	o	±
Haemolytic............	20–80	1.0–4.0	N	N	+	o	±	±	N	+	+	±	H	+	N-H	H	N	o	o	±
Familial haemolytic jaundice.	30–70	1.5–4.0	N-H	N-H	+	o	o	$+^3$	D	$+^3$	$+^3$	±	H	$+^3$	N	N	N	o	o	+
Sickle cell..............	20–90	1.5–4.5	N	N	$+^2$	$+^2$	+	+	N-D	$+^2$	$+^2$	$+^2$	H	+	H	N-H	N	o	o	o
Lead poisoning..........	50–90	3.0–5.0	N-L	N-L	±	o	o	±	N-	$+^2$	$+^2$	+	N-H	±	H	N	N	o	o	o
Banti's disease..........	25–50	2.0–3.5	L	L	±	+	o	+	P	o	o	o	N	o	L	L	V	o	o	+
Thrombopenic purpura....	50–90	2.5–5.0	N	N	o	o	o	o	N	±	o	o	N	o	V	L-o	N	o	o	o
Acute leukaemia.........	20–60	1.0–3.0	N	N	+	±	±	+	N	+	+	$+^2$	N	o	V	L-o	N	o	o	+

The data apply to average cases in whom the disease is well marked but not of maximum severity. There are numerous exceptions and variations (see text).

D = Dark.
H = High or increased.
L = Low or decreased.
N = Normal or not characteristically altered.
P = Pale.
V = Variable.
+ = Present or increased.
± = Inconstant or sparse.
o = Absent or sparse.

The platelets are much increased.

The red cell count is reduced, and is usually from 1.0 to 3.0 million. The mean corpuscular volume ahd haemoglobin content are about

normal. Immature red cells are increased, and normoblasts are constantly present, often in fairly large number; rarely, a few megaloblasts.

DeLangen and Lichtenstein (1936) state that myelogenous leukaemias are regularly found in the tropics that they are often overlooked or diagnosed as chronic malaria with a large splenic tumor. They also say that lymphatic leukaemias are extremely rare and they have never seen a case in the Dutch East Indies.

Bronchial Spirochaetosis.—Since the reporting by Castellani of this type of respiratory disturbance, it has been found to be widely distributed in temperate climates as well as tropical ones. Johnson, in Nigeria, reported bronchial spirochaetes in 107 of 147 sputa but he notes that these organisms were found in typical cases of acute bronchitis, pneumonia, pleurisy, asthma and pulmonary tuberculosis. Castellani has reported various spirochaetes as present (*B. bronchialis*, *B. buccalis*, *B. vincenti* and species of *Treponema*) and associated with these such organisms as streptococci, pneumococci, and the fusiform bacillus. Clinically, he divides the cases into acute and chronic broncho-spirochaetosis and the chronic group into (1) muco-haemorrhagic or muco-purulent haemorrhagic cases, (2) types with purulent expectoration and (3) types with putrid expectoration. There is also an asthmatic type and he recognized mixed infections with tuberculosis and broncho-mycosis. Many cases show patchy areas of consolidation. Castellani has found in treatment arsenic, tartar emetic and potassium iodide the drugs of importance. Korthof in Batavia in 96 cases of bronchial disturbance found in the sputum in 29 *B. tuberculosis* and in 6 "*Treponema bronchialis.*" DeLangen recognizes bronchial spirochaetosis as a distinct affection. However, Manson-Bahr does not seem convinced that this is a disease entity. David T. Smith (1927) concludes that we have a group of unrelated pulmonary conditions in which spirochaetes, fusiform bacilli and cocci are present. In his opinion the spirochaetes in the sputum are identical with those found in the buccal and pharyngeal cavity. He produced spirochaetal infections in laboratory animals by the intratracheal inoculation of gingival spirochaetes of patients with pyorrhoea. In 12 cases of primary bronchiectasis he found the fusiform bacilli and spirochaetes in all. The spirochaetal findings were noted in lung abscess following tonsillectomy, other lung abscesses, unresolved pneumonias, various types of bronchitis, bronchiectasis and tuberculosis. As would be expected the symptomatology was protean. Brain abscess and empyema are the most important complications, see also pp. 1100 and 1595.

Cerebrospinal Fever.—At the close of the Spanish-American War United States infantry troops returning from Cuba were ordered into barracks at Fort Cook, Nebraska, where during the cold winter months a large number of recruits were also received into the regiment. Daily drills and military maneuvers requiring considerable physical exertion were performed. The winter was a cold one and the troops were somewhat overcrowded in the barracks. A severe epidemic of cerebrospinal meningitis with a high mortality took place. The disease was diagnosed

by the writer bacteriologically and at autopsy. When the troops were ordered to proceed to Manila by transport at the time of the Philippine invasion, the epidemic ended. Only a single case of the disease appeared among the troops after their departure from the Fort. The epidemiology of this disease also received exceptional consideration during the recent war, and the outstanding factors in outbreaks seemed to be fatigue, overcrowding and lessened sunlight. With the commencement of summer, when the troops could be quartered in tents or buildings open to prevailing winds the prevalence of the disease fell, not to return in serious proportion until the following winter with cold wet weather, depressing influences and lack of proper ventilation. Zealous officers, impatient of delay, often drilled the men to the point of inducing excessive fatigue, particularly in raw recruits unaccustomed to strenuous military drill. From the above it would seem that conditions for the occurrence of this disease in the tropics were unfavorable.

However some outbreaks have been reported of considerable size notably in the southern Sudan. In Manila in 1925 there were 28 cases and 17 deaths and in the Central American hospitals of the United Fruit Co. in 1927, seven cases with 4 deaths were reported.

One who has never lived in the tropics cannot appreciate the intense discomfort, and even suffering, of the natives during periods of a marked drop from the usual temperature—even the European hunts up warmer clothing during a typhoon and the natives huddle in their houses, closing every avenue of ventilation, to keep themselves warm. Depressing influences are somewhat similar whether in Northern Europe or in the tropics.

Cirrhosis of the Liver.—A number of observers have emphasized the frequency of cirrhosis of the liver with ascites among native races. The subject has been one of especial study by an International Commission for Geographical Pathology. The Dutch pathologists and physicians have reported that of the various types of liver cirrhosis observed especially in the Dutch East Indies that the Laennec type is the most important. Next to this they place luetic cirrhosis, or syphilis of the liver, and finally cirrhosis resulting from clonorchiasis and schistosomiasis in regions where these conditions are endemic. They found the cirrhosis of Laennec exceedingly prevalent in Java and Sumatra and they emphasize that alcohol can play no part in it, since the native drinks but little spirituous liquor. The etiology of the condition is far from being clear and to what extent chronic malaria may be responsible is not evident. Some observers have suggested that the absorption of toxins from the large intestine in chronic bacillary dysentery or in amoebic dysentery may be a factor: others that it is influenced by the excess of highly and hotly spiced foods. The Dutch observers have suggested that it may arise from chronic intoxication in a liver deprived of glycogen or in undernourishment and starvation.

Since Mallory and Askanazy have called attention to the presence of copper in cirrhotic livers, this has been studied at Batavia. In an occa-

sional case, an increased amount of copper was found but it was absent in the majority of cases of cirrhosis.

The clinical picture does not differ from that seen in Europe. Many cases were successfully treated with salyrgan and ammonium chloride.

In addition to the prevalence of cirrhosis of the liver, primary carcinoma of the liver is frequently found in natives, frequently associated with previously existing cirrhotic changes.

Gall Stones.—The rarity of gall stones or of the clinical picture of cholelithiasis and cholecystitis among the natives of the tropics is well recognized. Kouwenaar found gall stones at autopsy in Javanese males, 1.78%; for females, 2.8%; and for Chinese, 3.86%.

In Europe the majority of the stones contain cholesterin (from 60–95%). The stones examined in Batavia by DeLangen have been bilirubin-limesalt stones containing only from 2–11% of cholesterin which seldom give rise to clinical symptoms of gallstones and are not facetted as are cholestrin stones.

Dental Conditions.—For some reason the dental surgeons practicing in the tropics do not seem to have reported variations in frequency or character of dental diseases from that encountered in temperate climates. This is rather remarkable in view of the influence dietary and hygienic conditions have on the teeth, and the explanation of the absence of reports in the literature, may be the lack of time and energy on the part of those best fitted to make observations.

After extensive correspondence with dental officers of the Navy, who had served on tropical stations, a few facts were gathered for Admiral Stitt by Commander Williams of the Naval Dental Corps.

Harvey failed to note any appreciable difference in the dental infections of white people residing in the tropics from conditions noted at home. There was often a complaint that caries had developed rapidly since coming to the tropics, but the only basis for such statement was in connection with coincident bad health from tropical diseases or environment. McCole, serving with troops in the tropics, during a period of two years, was unable to note any appreciable increase of dental caries. In the Philippines and Guam it was noted that the chewing of betel nut, to which is added a small piece of lime, causes marked attrition of the teeth, and fissuring of the enamel reaching to the pulp. This increases the incidence of caries, alveolar abscess and diseases of the pulp. The gums, however, are more seriously involved than the teeth.

Tichy has been impressed with the unusual inflammatory conditions of the attaching tissues of the teeth occurring in those serving in the tropics Many persons claim that an existing pyorrhoea had its inception during tropical service, and many complain that an existing pyorrhoea has assumed a more rapid course in the tropics.

The opinion seems general that Vincent's infection is more common and more difficult to treat in the tropics and, furthermore, the mucous membranes and the gums appear more susceptible to disease and respond more slowly to treatment. This is, apparently, also true of the healing

of tissues after extraction of teeth, of diseases of the pulp, and of pyorrhoea. McCole reports a marked increase in alveolar abscesses, but considers this as related to general body conditions in an unaccustomed environment.

Reed makes no comment on the incidence or progress of dental caries in relation to those indigenous or not indigenous to tropical countries, but observes that there exists a noticeable difference between dental problems encountered in the tropics and those ordinarily met with in the temperate zones. He enumerates the differences as follows, (1) a marked increase in the number of cases of spirochetosis of the mouth, (2) a greater virulency and extent in cases observed, (3) a delayed response to ordinary methods of medication, and increased susceptibility to post-operative infection and (4) the failure of accepted methods of treatment in the effort to retain pulpless teeth as useful units of the dental arch.

Diphtheria.—Formerly there was an idea that diphtheria, like scarlet fever, was extremely rare or unknown in the tropics. The assistance of the laboratory has shown that this old idea is incorrect and that the disease may be fairly prevalent in many tropical regions. It is more common in the Caucasian race. In tropical Africa according to the reports (from East Africa, Uganda, Tanganika and West Africa) it is rare and only sporadic cases occur.

Endocrine Disturbances.—Internists in all parts of the world are beginning to appreciate that many of the puzzling complaints of ill-health are connected with abnormal functioning of the ductless glands. The conditions resulting from excessive or diminished functioning of the thyroid gland are well understood and the determination of the basal metabolism rate is now a standard laboratory procedure. There are many types of apparatus on the market and the determination is within the reach of any hospital staff.

Hyperthyroidism is now rarely unrecognized as is also true of myxoedema but sub-states of thyroid functioning are less frequently recognized. The association of myxoedema in Chagas' disease is discussed in Chapter IV. The thyrotoxic heart may be produced by exposure to tropical conditions and may progress to a fatal issue. McCarrison has stressed the importance of endocrine disturbances in dietetic deficiencies and notes atrophy of all the glands of internal secretion in such conditions with the exception of the adrenal which tends to hypertrophy. There is possibly some hypertrophy of the pituitary in males. The oedema which accompanies most of the food deficiency diseases he associates with the adrenal enlargement and hyperactivity of function, although oedema does not invariably result from such hypertrophy. In pellagra there is a low blood pressure, possibly due to adrenal hypofunction. Goitre is found in many parts of the tropical world and Castellani states that this disease is met with frequently in Ceylon and various regions of Africa. It is common in some parts of Brazil where Chagas' disease is prevalent. Disturbances of the internal secretion of the pancreas, resulting in diabetes, are common in parts of Asia. The question of parathyroid dysfunction is discussed under sprue, Chap. XXXI. Sundstroem found that

the endocrine glands in the tropics exhibit a decrease of functional activity and that therefore a parallel decrease in blood sugar should take place. He observed that this actually occurred in Europeans of both sexes who had lived in the tropics since birth. Also a positive correlation was found between the sugar values and lecithin and cholesterol ratios in the blood. DeLangen and Schut, in Batavia, found that in the newly arrived European the blood sugar was augmented.

The importance of disturbances of endocrine functions is emphasized in so far as energy is concerned by the studies of Sundstroem and of Radsma on acid-base equilibrium basal metabolism. An alkalosis is present in the majority of tropical residents at the height of the hot season and may have an undesirable effect upon their physical well-being. However adequate water intake and muscular exercise may alleviate this alkalosis. Sundstroem found that the basal metabolism varied between 25.5 and 36.1 calories, with an average of 31. Variations in the dry- and wet-bulb temperatures may affect the level of basal metabolism in certain individuals. Radsma concludes that the basal metabolism in Europeans is reduced, or is, at least, lower than the standard values which obtain in Europe and America. See also p. 1694.

Focal Infections.—Attention has been directed to the importance of certain localized bacterial foci which may extend through blood or lymph channels and give rise to various systemic or localized diseases. Most important of these diseases are various types of arthritis together with endocarditis, myocarditis and pericarditis. Next in importance are renal infections, chiefly of the glomerulonephritis type.

Cholecystitis, appendicitis, pancreatitis and various skin lesions may also have origin in a focal infection. The primary foci may be localized in any part of the body but those seated in the tonsilar, peridental membrane, nasal and accessory sinus tissues are the most common and important. Focal infections of the genito-urinary tract may also give rise to generalized conditions as is also true of such foci in the alimentary tract. In the tonsils we should particularly examine the material of crypts for various streptococci and likewise the bacterial flora of tooth abscesses or pyorrhoea alveolaris.

TABLE SHOWING NUMBER OF TIMES EACH FOCUS WAS CONSIDERED A PROBABLE SOURCE OF INFECTION IN A SERIES STUDIED BY BILLINGS AND ASSOCIATES

	No.		No.
Tonsil	336	Prostate and genito-urinary tract	24
Teeth	136	Gallbladder	3
Sinus	12	Enterocolitis	2
Bronchi	5	Appendix	1
Uterus and tubes	12	Middle ear	1

Glanders.—This rare disease of Europe and the United States seems to be much more common in many tropical countries. In the Philippines

it sometimes showed itself in the acute form and has been much dreaded by reason of its great infectiousness. See melioidosis. (Chap. XX.)

Influenza.—In temperate climates we associate this disease with bronchial and coryzal manifestations. In the tropics types difficult to recognize are noted, especially the gastro-intestinal and a nervous one. The similarity in the clinical picture of dengue, with slight eruption in tropical influenza is striking. During the last pandemic of influenza there was a frequent complication of influenza pneumonia; many cases of this influenza-bronchopneumonia resembled plague pneumonia, and were sometimes confused with it by the uninitiated.

The disease is difficult to recognize during interepidemic periods on account of the lack of any distinctive physical signs. The onset is abrupt with a rapid rise of fever, headache, pains in the back and in the calf muscles, and a rather characteristic soreness of the eye muscles. There is a prostration which is often out of proportion to the other manifestations, and may be prolonged. There may be (rarely) an erythematous eruption. There is usually a leukopenia. Influenza, like measles, reduces the resistance to other infections, and secondary infections with the pneumococcus, streptococcus, and Pfeiffer's bacillus are common. In fatal cases death is due to these secondary invaders and rarely if ever to the influenza virus alone. In the great pandemics the cases occurring during the first outbreak are generally mild, whereas those in the succeeding outbreaks are attended with a higher mortality owing to the more frequent and severe secondary infections. This lowering of the resistance is indicated by the leukopenia and by the disappearance of the tuberculin reaction. The clinical picture in influenza is very similar to that of dengue and the dengue-like infections, and the diagnosis is particularly difficult in regions where these are prevalent.

Etiology. Bacillus Influenza—(*Haemophilus influenzae*) was originally isolated by Pfeiffer from the sputum and nasal passages of cases of influenza, and was believed by him to be the etiological agent of the disease. Recent work, however, has established the fact that a filtrable virus is the primary cause of the disease. Shope has shown that typical swine influenza can be produced in swine only when the influenza bacillus is inoculated together with the virus of influenza (human or swine) and it is possible that a similar relationship may exist in man. On the other hand, the disease can be transmitted to ferrets by inoculation with the swine or human virus alone, and is not modified by the addition of either the human or porcine influenza bacillus.

The evidence at present indicates that if this organism plays any part in the production of the disease it is purely a secondary one, and that a filtrable virus is the etiological agent.

In 1919 Nicolle and Lebailly obtained a disease in monkeys resembling human influenza by intranasal inoculation of filtered extracts of the blood and nasal secretions of influenza cases, but were unable to carry the infection through a second series of animals.

By using a susceptible animal, the ferret, Wilson, Smith, Andrewes and Laidlaw (1933) were able to produce a disease similar to influenza by

intranasal inoculation of filtered nasal secretions from influenza patients. They succeeded in transmitting it serially in ferrets by intranasal instillation and by contact. No other method of inoculation produced the disease. In these animals the virus was demonstrated only in the nasal mucous membrane. It is not found in the blood either in the inoculated animals or in human cases of the disease. Serum from these animals after recovery, and from human convalescents, neutralized the virus.

Andrewes et al. (1934) also produced the infection in mice by intranasal inoculation. In these animals the virus caused a bronchopneumonia similar to that which frequently occurs in human influenza, and the virus was demonstrated in the lungs with or without secondary invaders. The disease in mice was frequently fatal. The virus from human cases was not pathogenic for mice until it had been established in ferrets, and, therefore, mice are not suitable for isolating the human virus. On the other hand, both mice and ferrets are susceptible to the virus of swine influenza. Anaesthetization apparently renders the animal more susceptible and predisposes to the development of an extensive pneumonia. The virus isolated by these investigators from human influenza was shown by cross immunity tests to be related to (but not identical with) the virus of swine influenza. According to Shope, an animal which has recovered from either human or swine influenza is immune to both, but its serum protects only against the homologous virus. Swine influenza resembles the human disease also in the association of a Gram-negative bacillus (*Hemophilus influenzae suis*) with the virus. Shope has shown that the typical severe disease in swine depends upon the combined activity of both the virus and the bacterium. The virus alone causes only an ill-defined, mild, transient infection which is often afebrile, and the bacillus alone produces no ill effects.

The observations of Andrewes, Laidlaw and Smith (1935) and of Shope, Francis and others (1936) have shown that the viruses obtained from recent cases of human influenza, even from widely separated regions, may be identical with one another, but differ immunologically from that of swine influenza. They suggest, however, that the swine influenza virus is identical with the human virus of the pandemic of 1918. The disease appeared for the first time in swine in the United States at the beginning of the pandemic, and probably was transmitted to swine from man. These observers have found that the serum of a large proportion of adults examined who may have been infected at that time (but not of children under 12) contains antiviral substances for swine influenza, but in many cases not for the present human strains. Protective power for the human virus now prevalent, is common in children as well as in adults.

Immunity.—There is little or no natural immunity to influenza, as is shown by the enormous morbidity at the beginning of an epidemic. An attack of the disease produces some immunity. This has been regarded as only relative in degree and of short duration, because of the occurrence of a succession of outbreaks for two or three years after each of the great pandemics. If Shope's views are correct, however, the acquired immunity must be more substantial and enduring than has been believed. Further observations have proved the existence of viruses which are antigenically distinct, this may explain the apparent lack of immunity indicated by the epidemiological studies and some of the failures in protective inoculation.

Malignant Tumors.—It has been stated that malignant tumors are very rare among tropical natives. The proper solution of this question, however, was complicated by the frequent lack of careful autopsies.

Choisser, in Haiti, in a series of 524 consecutive autopsies, reported 17 or 3.24% of the cases dying as a result of malignant neoplasm. Of this number 14 died from carcinoma and 3 from sarcoma. (The tissue of origin of these tumors was as follows: 1 from lung, 2 uterus, 1 bladder, 1 rectum, 2 pancreas, 4 stomach, 3 breast, 1 lymph node, 1 leg, 1 face.)

During this period of investigation 342 biopsies were studied from operative material. Out of this number 64 or 18.72% proved to be

"cancer," 11 sarcomata and 53 carcinomata. The biopsy neoplasms included the following types of malignant tumors: 2 non-melanotic melanomas, 3 pigmented melanomas, 6 fibro-sarcomas, 27 squamous cell carcinomas, 23 adeno-carcinomas and 3 basal cell tumors.

The microscopic appearance of the cells of the various cancers differed in no way from that found in neoplasms of temperate climates. Many cell types were reported as anaplastic and apparently of the highest grade of malignancy. In such instances, one would expect early diffuse metastases in adjacent and distant organs, but it was surprising to observe when dealing with such highly malignant tumors to find that distant metastases were rarely encountered.

It is of interest to note that prior to this investigation, cancer in Haiti was considered extremely rare, as no cases were definitely proven from a microscopic standpoint to have existed. This did not indicate that the incidence of cancer was increasing there, but that scientific investigation had revealed a condition that was ever present but unrecorded.

Some statistics collected by Hoffman showed that cancer was almost eight times more prevalent in European clinics than among primitive races. This does not indicate that the primitive man enjoys an immunity. Such variation can be explained by the fact that little or no pathologic study has been done among the primitive, and also to the fact that a great proportion of primitive people do not live to the cancer-susceptible age.

Leonard Rogers, in a comparison of tumors in Calcutta and London, gives the following percentages: For Calcutta, benign tumors 42, malignant 58; while for London, the corresponding percentages are 43 and 57. As regards malignant growths, in Calcutta 18% were sarcoma and 39% carcinoma while the corresponding figures for London were 9 and 47.

Some striking variations in frequency of cancers were as follows, the first figure referring to Calcutta, the second to London: Tongue, 1.9—6.0; throat, 0.3—2; penis, 1.5—0.7; cervix, 6.7—1.8; breast, 6.8—15; uterus, 4.5—1.7; stomach, 0.4—1.1; large intestine, 0.7—3.3.

In concluding his study Rogers says that those who proclaim the rarity of malignant growths in native residents of the tropics must prove their assertions by accurate pathological data such as the figures he has given, which in 90% came from native Bengalis, living in villages under primitive conditions and on a diet of natural foods.

Malignant growths have also been shown to be common in the Dutch East Indies by DeLangen and Lichtenstein. In a series of 5000 autopsies, malignant growths were encountered in 9%, and the proportion of sarcomatous to cancerous tumors was 1 to 3.9, whereas in some European and American statistics it is 1 to 10. Sarcomata of the very malignant round cell type predominated. Malignant disease of the breast is not uncommon in the East African native and according to Vint, in almost 20% of the cases it is found in males. O'Connor has reported that in Bengal, melanotic sarcoma is commoner than in Europe. Primary liver carcinoma constitutes 12% of all carcinomata in the tropics (Vint) and in 90% of the cases is associated with cirrhosis (Snijders). The infre-

quency of gastric carcinomata is emphasized but carcinoma of the oesophagus is said to be common among the Chinese. The prevalence of skin carcinoma on the legs and feet following chronic ulceration is not common.

In Ceylon, the commonest malignant growth in both women and men between 35 and 50 is said to be cancer (epithelioma) of the cheek, and to be due to irritation caused by betel chewing. It is also common in South India.

In Kashmir, what is termed "kangri burn" (burn cancer) is found in the older men, where it is said that in the mission hospital 84% of the operations performed are for this condition. The kangri earthen ware bowl, 5–6 inches in diameter, is surrounded by basket work. It is heated by wood charcoal and is placed or even worn against the skin under a loose garment. The heat given out is estimated at 150–200°F. The epitheliomata usually appear in the scars of previous burns.

In Australia, epitheliomata of the face have been reported by Burrows and others in Scottish and Irish immigrants. The growths are said to be due to excessive irradiation by ultraviolet rays of the sun.

Measles.—Is not uncommon in a number of tropical countries. There does not seem to be any difference as to the symptoms and epidemiology of measles, whether in the tropics or in temperate climates. There have been numerous records of the devastating effects of the disease, when first occurring in a population previously exempt, and the usual explanation is that of inherited resistance. Squire in his account of the very fatal epidemic of measles, in Fiji, in 1874 when some 25,000 Fijians died attributed the great mortality to the fear that seized the natives, who abandoned their sick or subjected them to forms of treatment productive of serious complications. He states that we need invoke no special susceptibility of race or peculiarity of constitution to explain the great mortality—thousands were carried off by want of nourishment and care, as well as by dysentery and congestion of the lungs.

Mumps.—This disease is found in many parts of the tropics and presents similar features to the epidemic parotitis of temperate climates. In the Philippines there seem to be cases similar to mumps but without the contagious feature so characteristic of the disease in Europe.

Nervous System (Diseases of).—Encephalitis lethargica (Economos disease) has been reported in epidemics in Sarawak and in Cochin China. Encephalitis (Type B) is common in Japan and is apparently identical with the form found in St. Louis U. S. A. in which there has been absence of ocular lesions. Epidemics of anterior-poliomyelitis have been noted in a number of tropical countries and particularly in Africa, in Uganda and Kenya. Cerebrospinal meningitis has been referred to above. Sleeping sickness is discussed in Chap. III.

Pneumonia.—Just as with the tubercle bacillus so does the black race seem to have less resistance to the *Diplococcus pneumoniae* than does the white one. Great engineering works employing tropical natives are frequently associated with very fatal epidemics of pneumonia, especially

bronchopneumonia. Again in the black races the infection tends to become generalized rather than localized in the lungs. It is more toxic and insidious in its course than is true of the infection in the white man; it has the fatal trend of pneumonia of the aged. Another tendency is to invasion of the meninges. DeLangen has emphasized its prevalence and high mortality in the Malay race in the Dutch East Indies.

Pyogenic Infections in the Tropics.—The frequency of prickly heat in the tropics, and other causes of pruritus, as the bites of insects and mould infections, bring about scratching and transfer by the hands of staphylococcal and various other pyogenic organisms. Furunculosis is very common in the tropics and carbuncles seem to be more frequent than in temperate climates. There seems to be a tendency for these pyogenic infections to spread more widely and to invade the blood stream than is true in Europe or the United States. There are so many resistance-lowering factors in the tropics, as insomnia from the heat or biting insects, or skin irritations, that may lessen the vitality. The various diseases one is likely to contract in the tropics are many of them associated with a lowered opsonic index, and in the case of dengue, with its leucopenia, Stitt believes there may be a factor favoring the metastasis of local suppurative conditions to the kidney, liver, or other internal organ.

Tropical Impetigo.—Under the designation pemphigus contagiosus Manson described a very common skin disease of the tropics. The condition, however, is not the classical pemphigus. A bacteriological examination shows in a film from a vesicle great numbers of pus cells containing phagocytosed diplococci. Wherry named the organism *Diplococcus pemphigi contagiosi.* Culturally, this organism resembles *Staphylococcus aureus.* When in pus cells of an active inflammatory processes it may show a diplococcus morphology.

The disease is markedly contagious in children and is strikingly auto-inoculable so that unless the first lesion is treated immediately the eruption may become generalized. A small spot of erythema first appears which rapidly becomes vesicular, the bleb covering the entire spot, so that there is practically no surrounding inflammatory areola. The diaphanous covering rubs off with the slightest touch and leaves underneath a raw-looking surface which extends peripherally to form an angry-looking red patch an inch or more in diameter. In adults it rarely affects parts other than the axilla or crotch, occasionally the chest. The general health of the child is practically unaffected.

The usual treatment is with bichloride lotions followed by a dusting powder of equal parts of boric acid, starch and zinc oxide. An ointment of ammoniated mercury, 2% to 5% according to age, is the most satisfactory treatment.

G. Trovasos* (1942) has reported a form of pemphigus known in Brazil by the name of *fogo selvagem* or "wild fire," and that the etiology had been linked with a filterable virus. This form of pemphigus foliaceus is common in Brazil and its contagiousness is generally recognized. The clinical symptoms of it are the same as those found elsewhere, but the subjective phenomena itching, burning and acute pain, are much more severe and have given rise to the popular name for the condition. The disease has also been especially studied by J. P. Vieira† in São Paulo. Lindenberg, after failing to find a visible organism in pemphigus foliaceus, thought that a virus must be responsible for it and in 1937 he published successful experiments of transmission by injection into the testicles of serum from the blood of pemphigus cases. He also reported the transmission of the disease to guinea pigs. Vieira and his collaborators have not been able to confirm these results but are still continuing their investigations.

* Trovasos, V.: Bol. de la Oficina Sanit. Panamer., page 910, Sept. 1942.
† Vieira, J. P.: *Ibid.*, page 913, Sept. 1942.

The writer is not familiar with this Brazilian disease but he thinks there is a tropical contagious form of pemphigus in which the causative organism has not been demonstrated.

Tropical Boils.—It is interesting that the same organism responsible for this more fulminating lesion should be the one responsible for the common cosmopolitan boil and in fact boils are exceedingly common in the tropics. These boils may be larger and with a greater tendency to widespread distribution and in some regions they are so common as to have a regional designation (Nile boils). The staphylococcus of tropical impetigo seems to have greater virulence than that of the boils. Autogenous vaccines have sometimes been successful in the treatment of boils.

Rabies.—This cosmopolitan disease is common in addition to temperate regions in many parts of the Orient, India, Africa and parts of central South America. An unusual paralytic type of rabies in man and in cattle has been reported in Trinidad and also in South America. It has been shown to be transmitted by the bite of the vampire bat, *Desmodus rotundus* (Lima, 1934). Rabies is primarily a disease of dogs, wolves, cats and other carnivorous animals, but is communicable to man and domesticated animals through the salivary secretions of rabid animals. It is spread most commonly by bites, but infections have occurred from the licking of apparently normal skin by rabid dogs.

Epidemiologically, rabid dogs are almost exclusively the source of infection. Rabies has been eradicated from England by rigid quarantine of imported dogs. The saliva of the rabid dog may be infective five days before the onset of symptoms and remains so until the death of the animal. The first symptoms in the dog are change of disposition followed by excitability (even viciousness), and ending in paralysis and death within 10 days. Death follows development of symptoms invariably in man, and almost invariably in the dog, but the disease does not always develop from the bite. Clothing may absorb the saliva. Cornwall reported a series of 423 persons bitten by known rabid dogs. Of these cases 148 developed rabies. Lacerated bites about the face, neck or upper extremities are the most serious. In man the period of incubation is from 2 weeks to 6 months, usually less than 6 weeks. The first symptoms are irritability and depression, with early difficulty in deglutition. These are succeeded by extreme restlessness and hyperaesthesia. The dread of drinking water (hydrophobia) is due to painful reflex spasm. The temperature ranges from 100° to 102°F. The stage of excitement lasts about 2 or 3 days and is followed by a paralytic stage which lasts a few hours and ends in death.

Rabies is caused by a neurotropic *virus*, filtrable through all grades of Berkefeld filters. Inclusion (Negri) bodies are practically always demonstrable within the cytoplasm of the cerebral cells, but it is not known whether these bodies represent aggregates of the virus or cellular substances formed in response to its presence, or (probably) both.

After inoculation the virus apparently travels slowly to the central nervous system by way of the axis cylinders of the peripheral nerves. It has never been demonstrated in the blood. In the dog (seldom in man), the virus is constantly present in the saliva, and is believed to reach the salivary glands by way of the nerves.

The virus can be preserved for months in 50% glycerin. If frozen and desiccated rapidly, it maintains its virulence, but if dried at room temperature, it loses its virulence within a week. Marked differences in virulence occur in various strains of street virus, and may be produced by adapting it to different species of hosts, but all types are immunologically related.

Diagnosis.—The symptoms and death of a rabid dog are important points in diagnosis; therefore, the suspected animal should be kept under observation. If rabid, the dog will develop clinical evidence of the disease and die within 5 days. If it is killed prematurely the characteristic histological changes in the brain may not have developed sufficiently to permit a diagnosis to be made. When the animal dies, the head and several inches of the neck should be removed and sent to the nearest laboratory. The head may be packed in ice, or the brain can be removed, sectioned, and placed in equal parts of glycerin and water. (Sterilize the diluted glycerin by boiling and allow to cool.) This will preserve the virus for months. The diagnosis is made by the demonstration of the inclusion (Negri) bodies in the cytoplasm of the cells in the brain. These are practically constantly present and are characteristic of rabies.

The *Negri bodies* were first described by Negri in 1903. They are round or oval bodies from 1 to 20μ in diameter, which are present within the cytoplasm of the cerebral

cells. They may be found anywhere in the brain but are most numerous in the following areas, in order: (1) cornu Ammonis (hippocampus major), (2) region of fissure of Rolando (in the dog, crucial sulcus), or (3) cerebellum. In street rabies large forms from 18 to 23μ may be found, whereas in the nerve tissues of animals inoculated with "fixed" virus only minute forms, 0.5μ or less, may be detected. These bodies have been found four to seven days before the onset of symptoms.

The Negri bodies may be demonstrated by staining smears of the grey matter of the brain by some Romanowsky method, preferably by the Giemsa stain. The smears are made by mashing a thin slice of the outer grey matter rich in ganglion cells with a cover glass against the slide. Afterward the cover glass is gently drawn along the slide. Impression films may be used. The smears are then stained in the usual way.

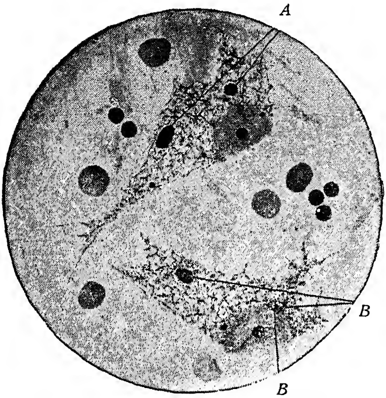

FIG. 395.—Two nerve cells of hippocampus major (smear preparation) showing *Negri bodies*. *A*, *Negri bodies*; *B*, inner bodies within the *Negri bodies*. (After Reichel, American Veterinary Review.)

The following method of staining is also good. The smear is fixed in methyl alcohol for 2 or 3 minutes, washed with water, and covered with a stain made by adding 3 drops of saturated alcoholic solution of basic fuchsin to 10 cc. of distilled water and then adding 2 cc. of Löffler's methylene blue solution. The stain on the slide is steamed gently, washed with water, and dried.

Since the relation of the bodies to the nerve cells is more or less disturbed in making smears, examination of stained sections is preferable. Fix a bit of brain tissue for 5 to 7 hours in Zenker's fluid, wash and dehydrate in graded alcohols and chloroform as usual, embed in paraffin, and cut sections. These may be stained with Giemsa's stain. The Negri bodies are brought out as lilac-red bodies in the blue cytoplasm of the nerve cells. It is necessary to differentiate in 95% alcohol.

Mann's stain may be used for smears or sections. After fixation in methyl alcohol the slides are immersed in the stain for 5 minutes and washed in distilled water. After passing through graded alcohols including two changes of absolute alcohol they are cleared in xylol. Better definition can be obtained by staining for from 12 to 24 hours and differentiating with alkaline alcohol (absolute alcohol 30 cc., sodium hydroxide, 1% in absolute alcohol 5 cc.). After 5 minutes, wash in absolute alcohol and then in water which may be slightly acidified with acetic acid. Dehydrate and clear in xylol. The stain is prepared as follows: Methylene blue (Gruebler 00), 1% aqueous solution, 35 cc.; eosin (Gruebler BA), 1% 35 cc.; distilled water, 100 cc.

By the Lentz method, the 3μ sections, after removal of the paraffin, are flooded with absolute alcohol. They are then stained with a 0.5% solution of eosin in 60% alcohol for one minute. Wash in water and stain for one minute in Löffler's methylene blue. Wash them again in water. Apply Lugol's solution to the section for one minute and then differentiate alternately in methyl alcohol and water until the section is pink. After washing in water, stain again with Löffler's methylene blue for one half minute, then wash in water and dry carefully with filter paper. Now differentiate in alkaline alcohol (1 drop *of a* 5% *solution* NaOH *in* 30 cc. absolute alcohol) until the section is pink, then quickly differentiate in acid alcohol (1 drop 50% acetic acid in 30 cc. absolute alcohol) until a slight blue outline to the ganglion cells is obtained. Treat rapidly with absolute alcohol and xylol and mount in balsam. The Negri bodies show as light carmine-pink bodies on the light-blue ground of the ganglion cells. This method can be used for brain smears also.

In addition to examining for the Negri bodies one may inoculate a rabbit or guinea pig subdurally with a salt solution emulsion of the brain. If the virus of rabies is present

the inoculated animal will develop symptoms within 3 weeks and Negri bodies can be demonstrated. This procedure checks the microscopical diagnosis and may replace it when decomposition prevents the demonstration of Negri bodies. Contaminating organisms may be killed by the glycerin so that inoculations are possible. When, from advanced putrefaction or other causes, the Negri bodies cannot be found, the changes in the Gasserian ganglia may give a diagnosis. In typical lesions the ganglion cells are more or less completely destroyed and replaced by cells of other types.

Local Treatment.—Thorough cauterization of the dog-bite wound with *pure nitric acid* (no other cautery is efficient), as soon as possible after the bite, is imperative, even when the Pasteur treatment can be given later. Immunization should be started immediately after the bite has occurred.

Pasteur Treatment.—By subdural inoculation of rabbits in series the virulence of the virus for rabbits is finally so increased that the rabbits die in six days. It is impossible to increase further the virulence of the virus, which is then termed "fixed virus." The pathogenic power of this virus for other animals is also changed so that it is not apt to cause rabies if injected subcutaneously.

To attenuate this virus, the spinal cord of the rabbit is removed and dried over caustic potash at a temperature of 23°C. The cord is divided into segments about 1 inch in length. Drying for about 15 days seems entirely to destroy the virus. To prepare the material for prophylactic injections a small portion of the cord is emulsified with normal salt solution. By the usual American method the first subcutaneous injection is of a cord which has been desiccated for 8 days. The treatment is given daily for about 20 days. The immunity is "active," and the immunizing agent is a "vaccine." The activity of the virus can be preserved for about a month by glycerin and cold storage.

Other methods of treatment are:

1. *The Harris Method.*—In this the brain and cord are frozen by means of CO_2 snow, ground up, and dried over H_2SO_4 for about two days. The virulence of the virus is reduced one-half. The virus, if kept at 0°C., retains the same potency for at least six months.

2. *The Cumming Method.*—In this the brain is emulsified in saline and dialyzed with formaldehyde solution. The virus is so attenuated that intracranial inoculation does not produce rabies.

3. *The Högyes Method.*—The fresh virulent cord is injected but so diluted in strength that it acts as an attenuated virus.

4. *Phenolized Method.*—Fermi, and more recently Semple, have used virus which has been inactivated by the application of strong (1% or 2%) phenol. Before injecting, the carbolized emulsion is diluted to preservative strength (0.5%). This method is now used extensively for man and for prophylactic immunization of dogs.

Antirabic serum has been prepared by injecting sheep with emulsions of rabbit's cord and brain, at first intravenously, then subcutaneously. This serum contains virus-neutralizing antibodies, but is valueless for treatment.

Rheumatic Fever and Scarlet Fever.—From a study of the statistical reports and from the writings of various authorities there would seem to be two cosmopolitan diseases, which are of extreme rarity in natives in the tropics, rheumatic fever and scarlet fever. It is true that in the Gold Coast report for 1911 there were noted 614 cases of rheumatic fever with one death. There does not, however, appear to have been any striking increase in admissions for valvular disease of the heart as would naturally be expected. In Calcutta, in 1911, there were 74 deaths from rheumatic fever.

While acute articular rheumatism is so widely distributed in many parts of the world, it occurs very infrequently among the natives that reside in hot, dry climates. Rheumatic valvular disease of the heart is

also rare in these localities. Manson-Bahr (1940) says that there are some who state they have never seen rheumatic fever or endocarditis in a life-long experience in India, Malaya, South China, and Central Africa, and MacKinnon reports that chorea was never observed in East African children. However, Chesterman, in Central Africa, has found it may occasionally occur. Acute rheumatism is sometimes observed in Europeans residing in tropical countries and in some localities with normal frequency.

As regards scarlet fever, statistical reports from various parts of the tropical world fail to show cases. In a report from Shanghai, which can hardly be considered as a tropical city, it has been reported that this disease first made its appearance in 1900, since which time it has spread among the Chinese, exhibiting at times marked virulence. Again, in Basutoland 67 cases were reported, but as this colony is in the extreme south of Africa it could hardly be called tropical.

DeLangen (1936) states scarlet fever does not appear in the East Indies and that while it occurs in northern China and India, it does not do so in the southern provinces. In South China, Zoller found that the Dick test gave uniformly negative results. In India, the disease is rare and of mild type, and especially attacks children. Megaw and Das Gupta reported that in India during 3 years scarlet fever was present in 212 districts but these cases were nearly all in Europeans. The few cases reported from Central Africa have been among European residents. On the other hand, according to Botticher (1934), sporadic outbreaks have occurred both in South America and the West Indies.

The Dick Test.—This test is used to determine susceptibility to scarlet fever and is carried out in the same manner as the Schick test for diphtheria. Over 80% of adults give a negative reaction to the toxin and have, therefore, a natural antitoxin (and perhaps other antibodies) in the blood. The test is usually positive during the early stages of scarlet fever and gradually disappears during convalescence.

A saline dilution of the standard toxin with a potency of one skin-test dose in 0.1 cc. is used. This is injected intradermally in the flexor surface of the forearm. Positive reactions appear in from four to twelve hours and are read in twenty-four hours. At the height of the positive reaction there is a circumscribed area of redness and infiltration varying from one to three or four centimeters in diameter according to the susceptibility of the individual. A reaction which has entirely faded in 24 hours is negative. Pseudoreactions are rare and controls are not necessary.

The Schultz-Charlton Reaction.—Antiscarlatinal serum or convalescent serum injected intradermally in an erythematous area will cause a definite and permanent blanching of the surrounding scarlatinal rash within five or six hours. This phenomenon is due to a local neutralization of the toxin. It occurs only in the scarlet fever exanthem and is, therefore, a useful diagnostic test in doubtful cases.

Sea-sickness.—This cosmopolitan disease has a particular application for the European visiting the tropics for two reasons: (1) It is apt to be the first illness encountered in making the voyage to the tropics. (2) It may be a serious matter for the tropical resident returning home should he encounter a storm and be sea-sick, as there is a proneness for such condi-

tions as latent malaria, sprue or dysentery to take on activity when the resistance is lowered; and in the depressed mental state and alimentary tract derangement of the sea-sick individual such effect may be profound. We have all noted the frequency of the vomiting of ascarids during a storm, showing most dramatically the upset of the alimentary tract. Again we rarely take sea-sickness seriously; so that a patient who combines some serious illness, as pernicious malaria, with his sea-sickness, is not apt to receive proper treatment during the period of the rough weather.

Butler in an article on sea-sickness gives the following facts as to etiology: Due to the observations by James that deaf mutes did not suffer from sea-sickness, and that of Kreidl, in which bilateral section of the 8th nerve prevented the sea-sickness syndrome, and finally the profound studies of Barany and others, during the late war, showed that the explanation of sea-sickness rested in disturbances of the movement of the endolymph in the semicircular canals, the innervating nerve (8th) having connections in the medulla with the cortex, cerebellum and anterior horn cells of the cord, as well as with the 3rd and 6th nerve nuclei and with the nucleus of the vagus and cells of origin of the phrenic nerve—thus can be explained nystagmus and vomiting. Faulty disturbances in the pressure of the endolymph gives rise to seasickness and when one has learned to compensate he acquires "sea legs." To avoid or lessen sea-sickness one should endeavor to make himself as fit as possible before going to sea—the farewell banquet is often the predisposing cause. It is well to eat sparingly and of simple foods for several days before embarking, and possibly to take some form of laxative pill. Most of the proprietary remedies have chlorbutanol (chloretone) as a basis, but it, like bromides or morphine, only acts as a depressant—it has no effect on the flow of impulses resulting from varying pressures in the semicircular canals. Dammert's method is supposed to be based on endocrine regulation, but a feature of the treatment is the administration of atropine, a questionable treatment. Percy and Hayden (1928) have recommended large doses of sodium nitrite (3 to 5 grains) every 2 hours until relief is experienced. The theory of this treatment is the depression of vestibular responses, but it would seem that the lowering of the blood pressure was the chief factor. There are, of course, certain dangers in rapidly lowering blood pressure. It is best to yield to the effects of sea-sickness, and to assume a recumbent position, on the right side, with the knees drawn up, better in a chair on deck. Some experience relief by taking deep breaths. Chairs which yield to motion in two directions have been recommended.

Smallpox.—This disease has justly been considered the greatest scourge of the natives of tropical countries. It is responsible for much of the blindness noted in natives of sections where vaccination has not been employed.

In some of the countries of the Orient smallpox killed more people than cholera, plague and dysentery together. Many reports have shown that as many as 80 to 90% of a native population may be attacked in an outbreak and of these practically one-half died. In such communities the

disease is more one of young children, the adults possessing a certain degree of immunity from attacks in childhood during previous epidemics. It has frequently been noted that the native colored races do not seem to acquire as marked an immunity as is observed among the white races of temperate climates following an attack of the disease. Again it has been insisted that the immunity following vaccination is not as marked as that obtaining in European countries. This point would seem not well founded because efficient and universal vaccination has apparently caused smallpox in the Philippines to be of no more importance than it is among any other well vaccinated people. It is striking to note the great number of pitted faces among adult Filipinos, whereas this condition is practically absent in the generation following the general vaccination introduced by the Americans.

In tropical natives the most severe forms of smallpox are observed —confluent and haemorrhagic. Opportunities for the spread of the disease are most favorable in many parts of the tropical world by reason of intimate association, religious festivals and pilgrimages. See p. 1684.

Under the name *alastrim* or Kaffir milk-pox, a disease similar to a mild form of smallpox has been reported from Africa and the West Indies. Various points were raised to differentiate it from smallpox, but in a recent epidemic in Jamaica and Haiti proof was adduced to demonstrate its identity with smallpox. In Haiti the epidemic was controlled by vaccination with smallpox vaccine, and those individuals exposed to the infection but properly vaccinated, uniformly escaped. Among the soldiers of the Marine Corps in Haiti there were only two cases and these occurred in men who gave no evidences of successful vaccination. The virus is contained not only in the skin lesions but also in the nasal and buccal secretions and the disease is communicable before the eruption appears. In spite of the mildness of alastrim, it must be regarded as a form of smallpox, and patients isolated and vaccination of contacts and others in the community performed.

Syphilis and Other Venereal Diseases.—Syphilis is rampant in many parts of the tropical world. Jeanselme has noted that syphilis among tropical natives often starts with an extra-genital lesion which tends to become phagedenic and that the secondaries are but slightly marked. It is in the tertiary stage that the disease shows itself in its malignancy.

All tropical workers have noted the absence of tabetic and paretic manifestations in the native syphilitics. Le Dantec notes that he has not observed parasyphilis in any European who had contracted syphilis from a native woman and brings up the question of a difference in strains of syphilis.

The American Naval Surgeons at Guam and Samoa have been struck with the absence of primary lesions of syphilis among the natives of these islands and Butler has suggested that this is due to an immunity received as result of contracting yaws in childhood. There certainly are many reasons for considering syphilis and yaws as closely related and this has been considered in Chapter XI.

DeLangen (1936) reports that in Indo-China the picture of hemiplegia with symptoms originating from changes in the arteries of the brain and spinal cord may be due to syphilis, which is true especially among the Chinese. Williams (1938), in Uganda, thought that syphilis was responsible for 53 out of 94 cases of heart disease. "Aortic syphilis" (aortic regurgitation) was present in 86 out of 894 post mortem examinations. More precise information on the subject is desirable.

Soft chancre is common in many tropical seaports and shows itself in a rather virulent form. In particular it is apt to be complicated by suppurating buboes.

Gonorrhoea is widely spread in the tropics, but the extent of its prevalence or the disability it causes is unknown. It is responsible for much ocular and arthritic infection and for much serious disease of female genitalia. In *tropical gonorrhoea* it would seem that involvement of the testicles is more common than in temperate climates.

Tetanus.—S. Bayne-Jones (1942) points out that as available statistics are incomplete the incidence of tetanus is not known in the United States. In 1939, for example, according to United States Public Health Reports, 31 states reported 474 cases of tetanus, apparently an occurrence of a small number among several millions of people. It appears that this infection has been far more prevalent in tropical than in temperate climates. It is particularly fatal in infants, the infection occurring from errors in the dressing of the cord at the time of childbirth.

Stitt has seen many cases of tetanus caused by the deep penetration of the barb-like tail of the sting ray, inflicted on persons wading in shallow waters of parts of the tropics, where these *Trygondiae* are found. These lacerated wounds furnish ideal conditions for contamination with soil and the development of the tetanus bacillus. In Central America it has been common after sand flea wounds.

During the World War, the incidence of tetanus among the British wounded was about 20 to 30 per 1000, before the routine administration of tetanus antitoxin, when it dropped to 1 or 2 per 1000. In the American wounded, where the experience of the British and French was available, the incidence was only 0.16 per 1000. Bayne-Jones attributes this low incidence in our American expeditionary forces to prophylactically administered antitoxin and also probably to the fact that no large number of our soldiers fought over the chalky and manured fields of the Somme region in the soil of which the tetanus bacillis is frequent.

Bacteriological Examination of a Wound.—Tetanus bacilli can rarely be demonstrated in films made directly from the wound. Animal inoculation is sometimes more dependable than cultural methods.

The wound should be curetted and some of the tissue fragments inserted into a pocket in the subcutaneous tissue of the thigh of a guinea pig. The remainder may be inoculated into glucose agar stabs or directly on Löffler's blood serum. On this medium the growth of contaminating organisms enables the tetanus bacilli to multiply aerobically. In these cultures the development of a foul, sour odor is suggestive. Films from such cultures frequently show the drum-stick spores. If these are found, heat

an emulsion of the growth to 80°C. for ½ hour to kill non-sporing bacteria, and inoculate a deep glucose agar tube, and cultivate anaerobically.

A more rapid method is to seal the material obtained in a capillary pipette, and heat to 80°C. for 15 minutes. This can then be plunged into a deep tube of glucose agar which is inoculated along the stab. The tube can be covered with sterile liquid petrolatum and incubated. However, better anaerobiosis can be obtained by the Buchner or Wright method.

The filtrate from cultures, even when mixed, can be inoculated into animals (rats or mice) to demonstrate the presence of the toxin. This may be the most reliable method for demonstrating the presence of tetanus bacilli. A control animal inoculated with the filtrate together with antitetanic serum should be protective.

Antitoxin.—The antitoxin is produced by injecting horses with increasing doses of tetanus toxin, at first adding sufficient antitoxin to neutralize it. A high degree of immunity to the toxin is developed. The method of standardization established by law in the U. S. is based on the work of Rosenau and Anderson at the U. S. Hygienic Laboratories. The antitoxin unit is defined as 10 times the minimal amount of serum necessary to protect a 350 gram guinea pig for 96 hours from 100 M.L.D. of a standard toxin. Standard antitoxin can be obtained from the National Institute of Health, by means of which others can determine the strength of their own toxin, and indirectly of their antitoxin. This unit has relatively 10 times the potency of the unit of diphtheria antitoxin.

Active immunization of human beings with tetanus toxoid offers the possibility of reducing the incidence of tetanus among troops to a minimum. According to Bayne-Jones the tetanus toxoid at present being employed by the United States Navy and Army is capable after subcutaneous injection, of causing human beings to produce tetanus antitoxin. Within 10 to 21 days after the last of a series of 2 to 3 subcutaneous injections of toxoid, individuals have shown from 0.05 to 2.5 American units of antitoxin per c.c. of serum. The average value is considerably above the level of 0.1 to 0.2 unit of antitoxin per c.c. of serum considered necessary for protection against a toxic infection. A single subcutaneous injection of toxoid administered a month after the last previous injection has a remarkable anamnestic effect in its ability to recall or reactivate the immune response. A third dose given 2 to 9 months after the second dose has produced as high as 12.5 American units of antitoxin per c.c. of serum. This response has occurred within 4 to 5 days as has been demonstrated especially by Cowles, Marvell and Parish. Confidence in this immunization procedure is so great that Circular Letters issued by the Surgeons General of the Army and Navy specify that prophylactic injections of tetanus antitoxin are to be given only to those who have not been vaccinated with toxoid.

Our Navy is using alum precipitated tetanus toxoid, while the Army is using plain liquid toxoid. Allergic reactions may occur after the injection of each type. Apparently less after alum precipitated toxoid than after liquid toxoid (Bayne-Jones). The reactions which occur, appear to be due to the hypersensitivity of certain individuals to proteins of the tetanus bacillus; to components of some brands of peptone used for the culture medium or to both.

Circular Letter Number 162, Office of The Surgeon General, Washington, D. C., November 20, 1942, gives the following instructions for active immunization against tetanus with tetanus toxoid.

a. Type of Toxoid. The material used is fluid, or plain, tetanus toxoid.

b. Method of Immunization.

(1) *Initial Immunization.*—This consists of a series of three subcutaneous injections of tetanus toxoid (plain), 1 cc. each, administered with intervals of three to four weeks between doses. This "initial immunization" produces an active immunity to tetanus. Subsequent reinforcement of this immunity is accomplished by the administration of a stimulating or recall dose of toxoid. The prophylactic use of tetanus antitoxin is therefore unnecessary after the completion of the initial immunization series. Instead, an emergency stimulating dose of tetanus toxoid should be administered as indicated below.

(2) *Subsequent Injections of Tetanus Toxoid.*—After the completion of the three injections included in the "initial immunization," a single "stimulating" dose of 1 cc. of tetanus toxoid will be injected subcutaneously as follows:

(*a*) Under normal conditions a "stimulating" dose will be administered at the end of the first year only, regardless of duration of service.

(*b*) A stimulating dose of tetanus toxoid (1 cc.) will be administered during the month prior to departure for a theatre of operations, unless such departure is within the six months' period subsequent to the completion of the initial series of three injections or within the six months' period subsequent to the administration of a stimulating dose.

(*c*) In addition to the above initial and subsequent immunizations, an emergency "stimulating" dose will be administered to those indicated below as soon as practicable after the injury (preferably within three days):

1. Individuals who incur wounds or severe burns on the battle field.
2. Patients undergoing secondary operations or manipulations of old wounds when deemed advisable by the responsible medical officer.
3. Others who incur punctured or lacerated wounds, severe burns, or other conditions which might be complicated by the introduction of *Cl. tetani* into the tissues.

Note. Passive Immunization against Tetanus by the Use of Tetanus Antitoxin.—Tetanus antitoxin will be used for the treatment of clinical tetanus, and when indicated, for the prevention of tetanus in individuals who have not previously been actively immunized with tetanus toxoid. The administration of tetanus antitoxin will be limited to the following:

(1) To patients presenting evidence of clinical tetanus.

(2) To individuals who incur wounds or other conditions which necessitate protection against tetanus, but who have not previously completed the initial immunization with tetanus toxoid as directed in paragraph *b.* above.

(3) To wounded individuals who may have been previously immunized, but whose records of immunization are lost or not available.

Individuals referred to in (2) and (3) above will be immunized passively with at least 1500 units of tetanus antitoxin and at the same time will be immunized with tetanus toxoid as directed in paragraph *b.* above.

Due consideration should always be given to the possibility of sensitivity reactions when injecting tetanus toxoid or tetanus antitoxin.

Clinical: In fully developed tetanus there is rigidity of neck and jaw muscles (trismus) and possibly involvement of facial muscles (risus sardonicus). Convulsions are apt to follow auditory or tactile stimuli. Cyanosis may result from spasm of the glottis. There may be moderate fever and leucocytosis. Symbiosis with other anaerobes or with various pyogenic organisms aids the development of tetanus bacilli and necrotic tissue is also of importance for which reason debridement became a routine measure during the last World War. Symptoms may appear in about two weeks after infection, shorter periods are more often attended by fatal results. There is a chronic form of tetanus which may occur several

months or longer after injury; or it may possibly follow late operations in the area involved. The soluble toxin elaborated in the infected wound may ascend by the axis cylinder of the nerves. Very extensive studies have been carried on with reference to the chemical nature of the tetanus toxin (tetanospasmin) and how it is transported in the body and how it acts. In the United States they have been carried on especially by John J. Abel, Firor and their associates, Mueller, and by Bayne-Jones.* These studies are too extensive and too diverse to be considered in this text book. The reader is referred to the article by Bayne-Jones (1942) in which the important progress made has been summarized. He reports that the central problem in the chemotherapy of tetanus is the search for chemical antidotes to the poison itself or to the nerve stimulating substances released and attributed through its action.

Treatment.—Rest in a darkened quiet room is indicated and it is essential that the patient be kept quiet and relaxed by the use of sedative drugs to prevent exhaustion.

Technical Manual, Guides to Therapy for Medical Officers, War Department, Washington, D. C., March 20, 1942 advises for treatment:

"(1) At the appearance of the earliest signs of tetanus, immediate therapy is indicated; all cases must be treated vigorously.

(2) The patient should be secluded, if possible, in a quiet, darkened room.

(3) Spasms must be controlled by heavy doses or either paraldehyde or chloral hydrate. Patients with tetanus vary widely in their response to these drugs and each case must be treated individually. From 8 to 40 cc. of paraldehyde can be given by rectum, and this dose can be repeated every 4 hours. Chloral hydrate can be given in doses of from 1 to 3 grams, either by mouth or rectum; this dose can be repeated every 4 hours or more often if necessary to control spasms. In severe cases, 0.03 to 0.06 gram (½ to 1 grain) avertin per kilogram of body weight should be given by rectum. With all these sedatives, care must be exercised to avoid marked respiratory depression. This heavy sedation is continued during the course of the severe phase of tetanus. If respirations cease, it is imperative to use artificial respiration.

(4) The primary wound should be treated as follows: the area around the injury is infiltrated with from 5,000 to 10,000 units of tetanus antitoxin, due precautions being taken against serum sensitivity. An hour later the wound is incised and left open; foreign bodies must be removed and adequate debridement carried out, when indicated.

(5) Tetanus antitoxin must be administered early and in adequate amounts. If the patient is sensitive to serum, desensitization should be carried out, when feasible. A syringe containing a 1:1000 solution of epinephrine (adrenalin) should always be at hand. The schedule of dosage for antitoxin is as follows: 60,000 units is given intravenously and 40,000 units intraspinally (in severe cases the intravenous dose is repeated in 24 hours); on the second day and every day thereafter until definite improvement occurs, approximately 5,000 units is given intravenously. The intravenous and intraspinal injections must be given *very* slowly. If anaphylactic symptoms develop during treatment, immediate withdrawal of the needle is imperative and frequent doses (0.5 to 1.0 cc.) of a 1:1000 solution of epinephrine (adrenalin) should be given.

(6) Tracheotomy should be performed if laryngeal spasm is causing suffocation.

(7) A liberal fluid diet (2,000 to 4,000 calories) should be given, and the patient must be kept in fluid balance.

(8) Constant nursing care should be provided, if possible."

* S. Bayne-Jones, Tetanus: *Proceedings of the Institute of Medicine of Chicago.* **14**, No. 3, April 15, 1942.

Serum treatment after symptoms have developed is far less efficacious than that of diphtheria, largely because the toxin has already become fixed to the nerve tissues. The nerve cells have a greater affinity for the txino than has the antitoxin, and when once injured do not recover as radiely as other body cells. The mortality of untreated cases developing within 10 days is over 80%. Bayne-Jones points out that serum therapy of tetanus is unsatisfactory at best. Abel and Chalian showed that anti-tetanic serum is powerless to mitigate or abolish existing and clearly evident symptoms of a descending tetanus in animals and in human being whose tissues had fixed one or more lethal doses of the toxin before the serum was used. It is hence obvious that the discovery of a relatively specific chemotherapy is urgently needed.

A few chemotherapeutic experiments have been performed in which sulfanilamide and sulfapyridine have been applied locally in animals with the idea of destroying the infecting micro-organisms. However Welch, Slocum and Herwick,* (1942) have found that sulfanilamide contaminated with tetanus spores and implanted in guinea pigs will not protect these animals from the development of tetanus. They hence emphasize that the sulfanilamide may act as a tissue debilitant in the presence of the tetanus bacillus and be conducive to the development of tetanus.

Trachoma.—It is often stated that this serious and very chronic eye condition is widely prevalent in the tropics. It is most frequent in Arabia and Palestine and in Egypt fully 95 per cent of the native population is affected (MacCallan). It is also endemic in Syria, Persia, Central Asia, China and Japan. It has been prevalent in eastern Europe and especially in Gallipoli, Poland, Lithuania, Russia and in southern Italy. The climate in a number of countries in which it occurs is temperate. In

* *Jl. A. M. A.* 120, 361, October 3, 1942.

discussing with naval ophthalmologists who have had extensive experience in the Philippines, Haiti and other tropical regions, Stitt was informed that the cases diagnosed by many general practitioners as trachoma are really cases of folliculosis, and that true trachoma is very rare in these countries—there is not the scarring so characteristic of trachoma. Not only do flies and other insects tend to spread acute epidemic conjunctivitis but the abundance of irritating tropical pollens brings about other conjunctival inflammations, as folliculosis.

The prevention of the entrance of trachoma by immigrants into this country has been one of the serious problems of the immigration offices of the public health service.

The relation of trachoma to the Prowazek bodies and to the Koch-Weeks bacillus is still under discussion and this is likewise true of the Gram-negative bacillus reported by Noguchi as the cause of trachoma. It has even been suggested that trachoma may be another example of a disease where food deficiency furnishes a background if not a cause. The reports regarding a rickettsial origin are discussed in Chap. XXV, p. 926.

Tuberculosis.—The negro race seems to possess a greater susceptibility to tuberculosis than the white one, a fact well recognized in the United States, where the colored population suffers far more severely than their white neighbors. The yellow races also show marked susceptibility to the scourge and in the Philippines it is easily the greatest cause of death. The mortality statistics of the Philippine Islands during 10 years compared the relative importance of the two diseases, tuberculosis and leprosy. According to this report, out of every 1000 inhabitants, 54.1 died in the course of the 10 years from tuberculosis, while 0.27 died of leprosy.

DeLangen (1936) states that in Netherlands India in earlier years tuberculosis stood fourth in the list of causes of death, following malaria, cholera and typhoid fever. After cholera was largely stamped out it rose to the third place and in the past year has displaced typhoid fever to the second place. He believes that in the near future it will become the most important cause of death in the East Indies.

The rapidity of its spread and the malignancy of its course when it was first introduced in the Pacific Islands has been vividly described by Robert Louis Stevenson in the Marquesan Islands. Its disastrous spread also occurred elsewhere in these islands notably in Samoa and Tonga. Today it is regarded as the chief cause of death not only in the Philippines but in Jamaica and in Africa on the Gold Coast, the Congo, and in Tanganyika. Scott has shown that there has been an enormous increase in its prevalence during the last 10 years, and in some cases, as in Nigeria and British Guiana, it has increased 5 and 6 times what it was previously.

In tropical regions the natives of the sea-level regions suffer more than those of the mountain plateaus and where the humidity is high rather than in arid sections. Thus tuberculosis is very rare or almost unknown in the dry desert-like regions of upper Egypt and the Sahara desert. The disease gains headway in the tropics in the rainy season and diminishes in prevalence during the dry season. One factor in the great spread of the

disease is the intimate contact of natives living together in a small room.

It is generally recognized that susceptibility is greater in childhood and that infection by way of the alimentary tract is common in children. When one notes the habit of expectorating anywhere and everywhere on the part of people untrained in hygienic rules, it is easy to recognize the opportunity babies and young children have of ingesting tuberculous material taken up on their hands while they are crawling about.

During the war there was a great deal of tuberculosis among the native African troops serving in France, and a study of the disease in these men has furnished us information as to the existence of two clinical types among them. In the soldiers from Morocco and Algiers, the type observed was similar to that occurring in Europeans, and this was explained on the basis of the opportunity that had been given the people of the areas from which the troops came to acquire tuberculosis from contact with white colonists and during a period of many years to have acquired a certain degree of resistance to the invasion of the tubercle bacillus.

In connection with the Senegalese troops and some others coming from sections of Africa where tuberculosis was rare or nonexistent, another type was observed which corresponded with the tuberculosis one often sees in a young child or a guinea pig. In these cases the disease was believed to start with enlargement of the glands at the roots of the lungs. This view of course would require examination by an X-ray plate for confirmation but it was found that the enlargement of the supraclavicular glands at a point near the insertion of the sternocleidomastoid was one of the best early signs. The glandular stage lasted about five to ten weeks during which time the general health did not seem to be materially impaired. Following this stage and lasting only about two weeks or up to two months a stage of generalized tuberculosis set in with fever, emaciation, caseous pneumonia or manifestations of miliary tuberculosis. There was no tendency to fibrosis or cure of the process, death almost invariably occurring. Borrel, who studied the disease in these natives, states that if put at rest and placed on a generous diet, while the case is in the glandular stage, one-half of them may recover. It was noted that sputum examinations of these cases were almost invariably negative.

Opie (1941) and his associates have carried out most important studies on the spread of tuberculosis in negro families of Jamaica, W. I. They found that "tuberculosis in the negro race of Jamaica pursues a much more rapid course than that in white people of European extraction and is readily transferred from a person with the disease to other members of the household, adults as well as children, so that many of them may die of tuberculosis within 2 years after it has been introduced into the family.

Of those who suffer from pulmonary tuberculosis in Jamaica, almost all disseminate tubercle bacilli, the proportion of those who have tubercle bacilli in the sputum being much greater than that of white persons of the United States (Philadelphia) and greater than that of American negroes.

Factors that promote the spread of the disease in Jamaica are the large number of tubercle bacilli in the sputum of those who suffer with rapidly progressive ulcerating lesions, uncleanly habits, unhygienic housing conditions, and lack of facilities for segregation of those who suffer with the disease.

In negro adults of Jamaica, infiltrating pulmonary lesions of the childhood or first infection type are found more frequently than in American negroes and much more frequently than in white adults." (Studies on Tuberculosis, the Johns Hopkins Press, Balt., 1941.)

Typhoid Fever.—When reliance for diagnosis rested almost solely on clinical manifestations, it was held that typhoid fever was rare or unknown in the tropics.

Since the advent of laboratory methods of diagnosis it has become known that typhoid and the paratyphoid fevers are quite common. The paratyphoid infections are more common in the tropics than in the temperate regions. The fever course and clinical picture of typhoid in the tropics are sometimes distinctly atypical. It was formerly common to consider cases of typhoid as malaria and in the southern states of the United States it was a common thing to diagnose typho-malarial fever. Of course, latent malaria is apt to flare up in a person sick with typhoid, but the idea that there was a symptom-complex partaking of the characteristics of typhoid fever and malaria is now grouped with historical data.

It is a remarkable fact that in many of the cities of the Orient conditions favoring infection with typhoid fever, such as neglect of the most elementary measures of disposal of faeces and lack of safeguarding of water supplies, exist and yet the natives seem to have an immunity to organisms causing alimentary tract diseases. It may be that such immunity is acquired by attacks of the disease in childhood. Certainly, Europeans in such communities have no protection unless sometimes it is acquired by vaccination. It should be remembered that protection from vaccination against the enteric group of bacteria can not be relied on for longer than a period of two years. It would seem that typhoid fever in tropical countries is sometimes more serious than in temperate climates—thus the death rate in India has been about twice as great.

In the absence of laboratory tests the chief reliance in the clinical diagnosis of typhoid should rest in the rather gradual onset of a continued fever, with a rather apathetic toxaemia. Of course atypical cases may have a fairly abrupt onset. An important point in the diagnosis is the rather slow pulse rate for the temperature elevation.

Marris's Atropine Test.—Manson-Bahr (1940) regards the Marris atropine test as of great value in the diagnosis of the enteric group of fevers. In this test one gives a hypodermic injection of grain 1/33 of atropine sulphate. Should the case be typhoid or paratyphoid the pulse rate is practically uninfluenced during the period from 25 to 50 minutes after the injection. Should there be any rise at all, it is said to be less than 14 beats per minute. In other infections or in normal individuals, the

pulse rate drops at first, but after 10 or 15 minutes rises to exceed the pulse rate before injection, by at least 15 beats per minute or 30 or 40 beats during the period of 25 to 50 minutes following the injection. The writer has no experience in the use of this test in diagnosis. It is not clear that it could depend upon any specific phenomena. Stitt and Clough (1938) give the following procedures for laboratory diagnosis.

Laboratory Diagnosis. BLOOD CULTURES.—*During the first week* of the disease typhoid bacilli can be isolated from the blood in about 90% of the cases. Positive cultures are obtained in from 70% to 60% in the second and third weeks, and after that time the percentage falls further. The organism should be identified culturally, and by agglutination with typhoid, paratyphoid A and paratyphoid B antisera. Occasionally a strain is not agglutinable when first isolated, but becomes so after a few subcultures.

STOOL CULTURES are occasionally positive early in the disease, but after the first week the typhoid bacillus may be isolated in most of the cases. The material is streaked over Endo, bismuth sulphite or Teague or brilliant green plates. When it is practicable to pass a duodenal tube, the typhoid bacillus can be isolated more readily by making cultures from the bile in the same way. Identification by serological as well as cultural methods is necessary.

URINE CULTURES are positive in about 25% of the cases after the second week. The urine should be centrifuged, and the sediment cultured, or broth flasks heavily inoculated. Plates of special media should be used unless the urine is obtained with aseptic precautions.

No patient should be released from isolation until cultures from the urine and faeces after catharsis, and preferably from the bile also, are negative. These methods are also used to detect carriers.

Widal Test.—After the second or third week the Widal test is the chief diagnostic aid. This should be repeated at intervals in order to detect any increase in the titer of the agglutinins. Cultures of known agglutinability must be used. In making the macroscopic tests it is customary for the sake of safety to use a suspension which has been killed by the addition of 0.1% of formalin. Such a suspension contains the H antigen only, but for clinical purposes it will usually suffice. Occasionally, however, only the O agglutinin develops in the body, and the Widal will not be positive unless a living culture or an alcoholized emulsion is used. Since typhoid and the paratyphoid fevers may be indistinguishable clinically, it is necessary to test the agglutination of these strains also with the serum. Some group agglutination of these organisms is very common in typhoid in the higher concentrations of the serum, but it is less marked than that with the typhoid bacillus, and is unusual in dilutions of over 1–40.

In individuals who have not received typhoid vaccine, agglutination with a 1–50 dilution of serum justifies a strong suspicion of typhoid fever, which is confirmed if the titer rises as the disease progresses. Agglutination in a dilution of 1–100 or more is practically diagnostic of active typhoid infection. Carriers may show some slight agglutination, but there is no important change in the titer of the serum on successive examinations.

If, however, the individual has previously received typhoid vaccine, difficulties arise in the interpretation of a positive agglutination test. Within a few days after vaccination the serum will usually show a high titer of specific agglutinins. This is followed by a fall in titer, at first rapid and later very gradual, so that over a short period the titer is practically unchanged. If such an individual develops typhoid fever the titer of the serum will increase as the disease progresses. This, however, may occur also in infections other than the typhoid fevers, as for instance in infections due to the pyogenic cocci or other bacteria—the so-called "anamestic reaction." One can only conclude that the results of the Widal reaction in vaccinated individuals must be interpreted with the greatest caution, even when the titer is high and rises with the progress of the disease. The reaction is of no value for the detection of carriers.

Prophylactic Vaccination.—The value of prophylactic vaccination as originally introduced by Wright has been amply demonstrated. The vaccine is prepared in the usual way and killed by heating to 53°C.

For many years most of the typhoid vaccine used in this country and in England was made from a single culture, "Rawlings," isolated by Wright in 1900. Grinnell (1932) has found that some cultures of this strain have become dissociated partially or completely, and have lost their virulence for mice. Vaccines from these cultures did not protect mice from infection with recently isolated, smooth strains as well as did vaccines made from a smooth strain, although vaccination with the Rawlings strain still produced somatic and flagellar agglutinins. He concluded, therefore, that virulent smooth strains should be substituted for the Rawlings strain for the production of vaccine, and that the demonstration of its ability to produce H and O agglutinins is not an adequate measure of its immunizing power.

This question has been investigated by Colonel Siler and his associates of the Army Medical Corps in an attempt to increase the protective properties of the typhoid vaccine used in the U. S. Army. In their experiments seven strains were tested, three of high virulence and four of low virulence. In cross-immunity tests mice vaccinated with virulent organisms were protected to a much higher degree than those receiving vaccines of low virulence. Of the virulent strains tested, one (No. 58) isolated from a chronic carrier of many years duration was the most effective, and this is now used in the preparation of the new vaccine. This is a smooth variant with high virulence and immunizing power, as tested by the production of active immunity in mice and protective power for mice of the serum of vaccinated individuals.

The employment of agglutination titer as a measure of immunity is unsatisfactory, because there is not a close parallelism between them. There is a marked difference in titer in different individuals after vaccination, and in a given individual, after reaching a peak in about 30 days, the agglutinin titer falls rapidly. Immunity may exist in the absence of agglutinins.

The more satisfactory mouse protection test was, therefore, used. It was found that with typhoid bacilli of low virulence such large doses had to be used to kill the controls that the treated mice were overwhelmed with foreign protein before resistance and immunity could be brought into play. If a virulent culture was used, and if the bacilli were suspended in 6% mucin and injected intraperitoneally, the M.L.D. ranged from 10 to 1000 organisms for the special strain of mice used, instead of 100,000,000 to 1,000,000,000, if suspended in Ringer's solution. In testing the protective power of the serum before vaccination a standard dose of culture of 10,000 living virulent organism was injected. If all the mice succumbed within 72 hours it was assumed that the man was not immune to typhoid fever.

Two methods of preparing vaccine were used; in one, the vaccine was heat killed and preserved with 0.25% tricresol; in the other, formalinized (0.1%). No distinct difference in the immunizing power of these vaccines was demonstrated. Vaccines were prepared by both methods from a culture of low virulence (the Rawlings intermediate strain which has been used in the Army for years) and from a highly virulent strain No. 58).

The subjects, who had not had typhoid fever and had not been vaccinated previously, were divided into four groups. Each received three subcutaneous injections of one of these vaccines. The first dose was 500,000,000, and the two subsequent doses 1,000,000,000 each. A statistical study of the results obtained showed a materially higher degree of protective power for mice when human immune serum following vaccination with *virulent organisms* was used than with organisms of *low virulence.*

Formerly a triple vaccine was used in the Army made up of 500,000,000 typhoid bacilli, 250,000,000 paratyphoid A bacilli and 250,000,000 paratyphoid B bacilli in 1 cc. of vaccine. The vaccine now in use contains only typhoid bacilli, 1,000,000,000 per 1 cc. The first dose is 0.5 cc., the second and third 1 cc. each. The vaccine is inoculated subcutaneously at intervals of one week.

From 1917 to 1924 triple vaccine was used in the Navy. Good statistical evidence showed that paratyphoid infections, other than cases of "food poisoning,," were rare

among naval personnel before paratyphoid vaccine was used. With the vaccine containing *E. typhosa* alone a larger amount of typhoid antigen can be used without undue risk of severe reactions with presumably greater protection against typhoid fever, which is the infection against which protection is principally required.

The U. S. Navy personnel receive two courses of three inoculations at intervals of 7 to 10 days, four years apart, of a vaccine containing approximately one billion typhoid baccilli per cc. The first dose is 0.5 cc., the second and third 1 cc. each.

There may be a slight rise in temperature (rarely above 101°F.) with headache and malaise in about half of those inoculated.

Agglutinins appear in the blood within a few days. By the end of a month titers of 1–640 or 1–1280 are frequently reached. The immunity produced is believed to last for from 2 to 5 years, and there is some evidence that it may last much longer.

Neither vaccines nor therapeutic sera have proved to be of any value in the treatment of typhoid fever. The studies of Magrassi (1940) on an alleged typhoid ultravirus are not conclusive.

The Paratyphoid Fevers.—The paratyphoids would seem to be more prevalent, in proportion to typhoid, in the tropics than in temperate climates, thus in India, of 1886 British soldiers, convalescent from enteric fevers, 791 were diagnosed as typhoid, 633 as paratyphoid A, 136 as paratyphoid B and 326 as enteric cases of uncertain etiology. Paratyphoid B cases seem more frequent in temperate climates than paratyphoid A ones, as noted during the war in France. Cruickshank, and Lafrenais, in a study of carriers, among the 1886 cases noted above observed that 49 became carriers and of these 34 were from paratyphoid A cases, 9 from typhoid convalescents and 6 from paratyphoid B convalescents. Of 13 chronic carriers (those carriers excreting organisms after a period of six months) 8 were carriers of paratyphoid A, 4 of typhoid and 1 of paratyphoid B. This evidence would indicate that paratyphoid A, once introduced, might spread more widely than the other enteric affections.

Clinically, paratyphoid A cases often resemble typhoid ones rather closely, although as a rule less severe in course. With paratyphoid B the course is less severe than with the other enteric organisms but it often shows an abrupt onset and is frequently similar to that in cases of meat poisoning. This organism and the Gärtner bacillus are common excitants of (so-called) "ptomaine poisoning." In paratyphoid B cases there is sometimes a tendency for the organism to localize in the pelvis of the kidney or elsewhere and it may cause a broncho-pneumonia.

A critical study by Miller brings out the following points: During the war paratyphoid A cases would be at one time more common and at another time paratyphoid B ones. The paratyphoid organisms may give rise to as serious manifestations as typhoid, which was particularly true of typhoid in the inoculated. As a result of the paratyphoid bacilli having a greater tendency to generalize there is less of the localization in the lymphatic tissues of the intestine than with typhoid. As a result many types of paratyphoid are noted. Among *typhoid types* the general manifestations greatly resemble typhoid but haemorrhage and perforation are much less frequent. The *dysenteric type* may in addition be associated with general symptoms. The *nephritic type* has been rather frequently noted;

this may be of the nature of nephritis or pyelitis. There is also a *rheumatic type* and an *influenzal* one and in this latter type there may be respiratory, gastrointestinal or nervous symptoms. Miller noted that the infectivity of paratyphoid was very great.

Colon Infections.—Such infections seem to be rare in temperate climates other than as localized conditions especially of the urinary bladder. Cholecystitis is not infrequently due to a colon bacillus infection. In the tropics, however, especially following bacillary dysentery, we may have a generalized infection which may result in a fatal septicaemia. In such cases abscess formation in the kidneys is usually found. Cases diagnosed as mild typhoid fever have as a result of blood cultures been found occasionally to be due to a colon bacteriaemia.

In temperate climates as well as in the tropics pyelitis is often due to a colon infection and probably 10% of cases of appendicitis are caused by the colon bacillus alone, although it is extremely frequent in association with streptococci or staphylococci.

Alcaligines Fecalis (*Bacillus Fecalis Alkaligines*) *Infections.*—Cases similar to typhoid fever have been reported to be due to infection with this member of the typhoid-colon group of organisms. It is a not uncommon inhabitant of the intestinal tract and does not appear usually to have any pathogenic action. However it has been isolated from the blood of a few cases which resembled typhoid and has agglutinated (1–50) with the sera of such cases, which did not show agglutination for typhoid. It has also been under suspicion as the cause of some cases of diarrhoea of children. Shearman, Hearst and others noted the isolation of *B. fecalis alkaligines* from the blood in suspected typhoid cases. The patients showed a sudden onset with slight chill, severe headache, nausea, and occasionally vomiting, with aching of the limbs. The fever would last 2 to 5 days, ranging from 101° to 102°F. with often a second pyrexial period.

Varicella.—This disease is of common occurrence in the tropics and does not seem to give rise to greater mortality than it does in temperate climates. In the Philippines Stitt was struck by the resemblance it bears to cases of varioloid, inasmuch as there was frequently noted as many lesions on the face as on the body. In fact he felt sure that the pustular lesions of the face of such cases were those of smallpox, until he later noted typical varicella lesions on the body.

Vincent's Angina.—While not rare in temperate climates, various affections of the oral mucous membrane due to the fusiform bacillus in symbiosis with spirochaetes are fairly common in the tropics. The best known condition is one in which the tonsils show somewhat the appearance of a follicular tonsillitis but ulceration is more common and severe, however, with less evidence of toxaemia.

The temperature in a case of pure Vincent's angina rarely exceeds 101°F. but if there is a mixed infection with other pyogenic organisms the temperature and other signs of a severe infection may be more marked. There is usually more or less swelling of tributary glands. Associated

with the angina or alone there may be a gingivitis in which the spongy gums more or less resemble those of scurvy or of pyorrhoea alveolaris. In fact spirochaetes have been considered as factors in the development of pyorrhoea alveolaris. In the tropics there have been many reports of organisms of the type of those described by Vincent occurring in a form of skin ulceration or in affections of the mucous membranes in addition to the oral ones, more particularly the pudendal mucous membranes. During the World War many soldiers were attacked with "trench mouth" or Vincent's infection.

The infections are readily and easily diagnosed by a film stained with any simple aniline dye. Care must be taken not to accept such a finding as the sole cause, as an underlying diphtheria, syphilis or other dyscrasia may be more important.

War Wounds.—In a study of the aerobic bacterial flora of war wounds Lawrence found that more than 80% of the discharges from such wounds showed streptococci, which especially flourished in deep pockets, staphylococci replacing them in shallow wounds. Gram-negative bacilli were present in 95% of smears. Of these, *E. coli* was present in 50% of cases. The combination of aerobes and anaerobes in a wound makes conditions more favorable for the anaerobes. Wounds contaminated with fusiform bacilli do badly.

The pus from wounds infected with anaerobes is usually very foul. The most important anaerobe in the discharge from gas gangrene wounds is *Cl. welchii.*

The anaerobic spore bearing bacilli which occurred with great frequency in wounds during the World War are common inhabitants of the intestinal tracts of man and other animals, and hence are frequently present in fertilized soils. The spores of most of these anaerobes develop in the intestine, and may remain viable for years in the soil. Cultures from the clothing of the men in the trenches almost always showed anaerobic organisms, especially the Welch bacillus and frequently tetanus bacilli.

Isolation of these organisms in pure culture is technically difficult. Repeated plating out of cultures is usually necessary, and Kendall regards the selection of a single spore by the Barber technique as essential for obtaining a pure culture. For diagnosis, see p. 1685.

The most important saccharolytic anaerobe which ferments carbohydrates vigorously with the production of acid and gas is *Clostridium welchii* the "gas bacillus." It was isolated from some 75% of the cases of gas gangrene during the World War. Several other species may also be encountered, particularly *C. oedematis maligni* (Vibrion septique). The local treatment of such lacerated wounds should consist of immediate "debridement" to render conditions unfavorable for the growth of the bacteria. Secondary infections of such lacerated wounds with *C. welchii* are very common in some tropical countries and post mortem invasion with this organism is frequent.

Technical Manual, Guides to Therapy for Medical Officers, War Department, Washington, D. C., No. 8-210, March 20, 1942 advises the following:

"**Gas-bacillus Infection.** *a. General.*—The problem of gas-bacillus infection is largely one of prevention, and all wounds in which such infection is a possibility should receive proper surgical treatment (par. 3) at the earliest possible moment.

b. Prophylaxis.—Sulfanilamide is recommended as the drug of choice, the initial dose being 6.0 grams (90 grains) oral and subsequent doses 1.0 gram (15 grains) every 4 hours day and night. This should be continued for 7 days or until definitive treatment is available. This period of therapy almost always eliminates the possibility of gas-bacillus infection. Crystalline sulfanilamide should be used *locally.* It should be distributed evenly over the surface of the wound, approximately .01 gram (1½ grains) being used per square inch but not over 10 grams (150 grains) for any one person.

c. Treatment. (1) *General.*—The primary wound should be opened, and *all* infected tissue should be removed (in occasional cases, this may be so extensive as to warrant amputation).

(2) *Chemotherapy.*—(*a*) Sulfathiazole is recommended at present as the drug of choice.

(*b*) The dosage is as follows:

1. *Initial Dose* (*Oral*).—6.0 grams (90 grains).
2. *Subsequent Doses* (*Oral*).—1.0 gram (15 grains) every 4 hours day and night until the temperature has been normal for 48 hours; then 0.5 gram (7½ grains) every 4 hours day and night until convalescence is completely established.

(3) *Serum Therapy.*—Polyvalent gas gangrene antitoxin should be used when in the opinion of the medical officer it is indicated. It should be administered in adequate dosage according to the directions inclosed in each individual package.

(4) *Local Chemotherapy.*—(*a*) If all grossly infected tissue cannot be surgically removed, sulfathiazole powder should be applied locally, being used in the same way as sulfanilamide powder (*b* above).

(*b*) If all grossly infected tissue appears to have been removed, a paste of zinc peroxide may be applied. This is made by mixing a medicinal grade of zinc peroxide with an approximately equal amount of sterile distilled water or physiologic saline solution, to form a smooth, creamy suspension, which flows readily to all parts of the wound. The wound is then covered with a thick layer of cotton, wet with water or saline solution, over which is placed a layer of rubber, cellophane, or vaseline gauze, to prevent evaporation. A fresh dressing should be applied every 1 or 2 days, washing out the exudate and old zinc peroxide with sterile physiologic saline solution, and these should be continued until the infection has been controlled."

APPENDIX

Section I

INDEX OF CLINICAL DIAGNOSIS

When a patient presents himself, the physician is confronted with the necessity of arriving at a working hypothesis which will ultimately lead to the establishment of a definite diagnosis. The difficulties of precise diagnosis and the augmented risks to life should an erroneous diagnosis be made are recognised and the clinician should allow no sign or symptom to go unchallenged, regardless of how insignificant it may seem. On account of the increasingly complex problem of diagnosis the physician may incline to depend more and more upon the laboratory and to be tempted to neglect the simpler art of physical diagnosis. The teachings of Osler should ever be kept in mind: To observe, palpate, percuss and auscultate.

As Fremont-Smith has aptly stated: "We forget that the accuracy of the laboratory is often specious, that many a disease cannot be detected chemically or serologically, and that time and again a diagnosis is written upon the very countenance of a patient, have we but the wit to recognise it. Diagnostician and criminal detective have this in common: that for each the discovery of a clue is a first and an essential step in the train of reasoning. Each in his own field must be quick to sense the possibilities suggested by the infinitesimal deviation from the normal; the detective by a blood stain or a bit of ash, the medical man by a tiny gland or a barely palpable spleen. Any square millimeter of body surface may offer a clue. Under appropriate circumstances a single macule may arouse suspicion of typhoid or measles, or of bacterial endocarditis."

It is not the desire to leave the impression that laboratory aid is not to be sought. On the other hand when intelligently used it is of the utmost importance and may be the only means of confirming or establishing a diagnosis. The majority of the diseases more common in tropical countries are of a specific nature and the demonstration of the specific organism decisive. However, one should keep in mind that the patient may be suffering from two or more diseases and this is especially true in the tropics. Practice in the tropics often must be carried on without the aid of large libraries and laboratories and it is for this reason that there has been inserted this section on symptom diagnosis. Patients seek medical aid for definite reasons and they usually present a grouping of symptoms which when carefully analyzed will be found to be diagnostic. In the following section the varying symptoms are defined and arranged in alphabetical order. Under each symptom the diseases are listed in which this particular symptom occurs and differential diagnostic data are included as an aid in arriving at a tentative diagnosis. The guiding principle in the use of this section should be to note all symptoms which have attracted special attention in a given case, ascertaining the diseases in which they occur and concisely to list these diseases as possibilities. In this manner we may generally arrive at a tentative diagnosis on the first examination. Following this procedure one may intelligently apply the necessary laboratory aids to establish the diagnosis definitely. Further observation of all symptoms, the careful analysis of the temperature curve, the use of the therapeutic tests, or a study of the course of the disease may be required in order to arrive at a definite diagnosis and to prognosticate with a sense of security.

Abortion.—The expulsion of the foetus before it is viable is a common occurrence in such diseases as syphilis, measles, relapsing fever, scarlet fever, small pox, undulant fever, food deficiency diseases, malaria, cholera and plague.

Albuminuria.—Persistent albuminuria is indicative of renal disease. Albuminuria may occur due to pus, blood and vaginal discharges contaminating the urine. Excessive muscular exercise, ingestion of large quantities of proteins and prolonged cold baths are common causes of transient albuminuria. Cyclic, orthostatic or postural albuminuria is fairly common in the young neuro-asthenic type of individual. Among the causes of albuminuria, the most common are altered blood pressure and altered kidney structure. Albuminuria is a common finding in infective fevers, genito-urinary haemorrhage, nephritis, nephrosis, infections of genito-urinary system and is of diagnostic aid in yellow fever and blackwater fever. It is indicative of kidney complications in diphtheria and scarlet fever.

Beriberi.—The absence of albumin in the urine in beriberi is important in differential diagnosis from acute nephritis.

Blackwater Fever.—In this disease there is a great abundance of albumin with haemoglobin. Albumin diminishes as the color of the urine clears up.

Malaria.—Albumin was present in 38% of benign tertian infections and 58% of malignant ones at Johns Hopkins Hospital. Several observers have recently emphasized the presence of albumin and casts in some 50 per cent of severe quartan infections. Among these are Boyd (1940), Amer. Jour. Trop. Med., p. 749.

Yellow Fever.—The disease in which this is of peculiar diagnostic and prognostic value is yellow fever. We expect albumin about the second day with a steady increase in amount during succeeding days of the fever. The degree of oliguria or the intervention of anuria is of greater prognostic value than the degree of albuminuria. The albuminuria is of great diagnostic value in differentiating yellow fever from dengue.

Amblyopia.—Dimness or blurring of vision occasionally occurs in malaria and in quinine therapeusis.

Malaria.—The plugging of the retinal arteries may lead to blindness which may be transient or lasting. The disc in plugging of retinal arteries by plasmodia is grayish red, distinguishing it from the pale white disc of quinine amblyopia.

Onchocerciasis may also lead to disturbances of vision and blindness in the advanced stages of the disease from keratitis and choriodoretinitis.

Wood alcohol, arsenic and bromide poisoning are other causes to be considered. Ophthalmoscopic examination should be made in all cases of complaint of dimness of vision.

Allergy.—The natural hypersensitiveness of an individual as contrasted with induced hypersensitiveness may be manifested by asthma, angioneurotic oedema, hay fever, intermittent hydrarthrosis, and urticaria.

Amenorrhoea.—The absence of menstruation when not a symptom of pregnancy may be produced by the menopause, acute infectious diseases, anaemia, tuberculosis, nervous affections, alcoholism, and it is also produced by change in climate. For some time after arriving in the tropics women may cease to menstruate for no obvious reason other than the change in climate, or menorrhagia may develop from the same cause.

Anaemia.—The deficiency in the quantity of blood (oligaemia) or in the quality, as a deficiency in haemoglobin (oligochromaemia), or in the diminution of the number of red blood cells (oligocythaemia), may be due to local or general conditions. Anaemia is accompanied by loss of energy, palpitation, cardiac murmurs, paleness of skin and mucous membranes, and other systemic symptoms depending upon the underlying cause of the anaemia. The van den Bergh test will differentiate anaemia due to excessive red blood cell destruction from that due to loss of blood from haemorrhage or secondary to other causes. In secondary anaemia the van den Bergh test is normal, while in anaemia due to the rapid destruction of red blood cells it is direct-delayed (negative direct—positive indirect), and the quantitative test gives a reading above normal. In excessive red blood cell destruction as in blackwater fever, malaria, and pernicious anaemia this test is of diagnostic value.

The cosmopolitan forms of anaemia are discussed in Chapter LIV, p. 1568.

The old idea that tropical life produced an anaemia is no longer held, the view now being that such anaemic conditions are almost invariably due to some recognized cause, the most important of which is malaria. Natives of the tropics may appear bleached

out but show a normal red count and haemoglobin percentage. Chamberlain's observations have shown that a residence in the tropics of approximately two years has no appreciable influence on the red cell count or haemoglobin content of the blood of white men and that the actinic rays do not seem to produce anaemia.

Ancylostomiasis.—In advanced cases of hookworm disease, showing a picture of profound anaemia, there may be so few worms present that the method of making diagnosis by finding ova may be unsuccessful. Ancylostomiasis is along with malaria the disease to be first thought of in connection with anaemia. It may be difficult to differentiate the anaemia of malarial cachexia from that due to hookworm disease.

Blackwater Fever.—The striking feature of blackwater fever from the condition of the blood, is the rapid and great reduction in red cells and haemoglobin. As a result of the haemoglobinuria we may have in a few days a fall of red cells from 4 or 5 million to approximately 1 million and of the haemoglobin to 20%. The color index is usually about 1. The blood is thin and the serum tinged. Probably from the excessive haemolysis one does not see degenerated cells as frequently as would be expected.

Helminthic Affections.—Not only hookworm disease, but other helminthic conditions are to be remembered as causes of anaemia. Very important among these are rectal and vesical schistosomiasis, as well as that from Japanese schistosomiasis, together with liver and lung fluke disease. Even the ordinary round-worm, *Ascaris lumbricoides*, is to be thought of in a tropical anaemia. Cases of anaemia, in which no other demonstrable cause has been noted, have been thought to be due to trichuriasis. Cases of *Diphyllobothrum latum* have sometimes been associated with severe anaemia.

Kala-azar.—This disease gives a marked anaemia with an earthy color of the skin. Leucopenia and splenic enlargement are characteristic and the finding of parasites confirmatory.

Liver Abscess.—The anaemia in liver abscess is usually not so great as the earthy complexion may indicate. The emaciation is greater than the anaemia.

Malarial Cachexia.—Although the malignant tertian infection has the greatest tendency to produce anaemia yet any type may, when untreated, bring about the more or less profound anaemia with earthy skin, enlarged spleen, dyspnoea on slight exertion, and oedema of the ankles characteristic of malarial cachexia.

Malta Fever.—This disease is usually followed by a moderate anaemia.

Onyalai.—Not infrequently gives rise in severe cases to an anaemia from epistaxis and haemorrhages elsewhere in the body, accompanied by a marked reduction in the number of blood platelets.

Oroya Fever.—In this disease there is what might be termed a fulminating pernicious anaemia. The rounded or rod-shaped organism which attacks the red cells seems to be peculiarly active in the bone marrow; excruciating bone pains being sometimes a feature of the disease. There may be a reduction in red cells to one million per cmm. within a few days. Normoblasts are abundant and megaloblasts may be observed in the more severe cases.

Sickle-cell Anaemia.—The red blood cells may be reduced to 2,000,000 in the active phase of the disease. Nucleated red cells and basophilia are present. There is a leucocytosis—17–50 thousand Jaundice is generally present. Laboratory diagnosis is made by finding the characteristic crescent shaped red blood cell. (Limited to negroes.)

Sprue.—There is considerable reduction in red cells which may fall below 2,000,000 in advanced cases. The white cells may show a slight tendency to leucopenia with a relative increase in lymphocytes. The haemoglobin is not as much reduced as the red cells so that we obtain a color index of from 1.1 to 1.3. Poikilocytosis and punctate basophilia are often noted, but rarely does one find nucleated red cells. In a severe case the blood picture is usually macrocytic like pernicious anaemia. Occasionally, however, it is hypochromic. The eosinophiles are rare or absent as the case advances. One often finds many (7–9) nodes in the polymorphonuclears. The response to oral treatment with liver extract is not so uniform and rapid as in the ddisonian pernicious anaemia.

Tropical dysenteries are often responsible for anaemia.

Trypanosomiasis.—As the disease progresses a secondary anaemia may result. The leucocyte count is usually normal but the differential count usually shows an

increase in the large mononuclears. Bacterial infections often supervene when a leucocytosis will be noted.

Anaemia, Pernicious.—Insidious onset; no marked malnutrition; lemon-yellow tint to skin; gastrointestinal disturbances; characteristic red, raw tongue and neurological manifestations. The following laboratory procedures are necessary to establish the diagnosis: complete blood picture including haemoglobin estimation, fragility test and reticulated count; van den Bergh test and stomach analysis after histamin, see p. 1573. The following procedure is an excellent one in a case of doubtful diagnosis. Administer daily 400 to 600 gms. of liver or its equivalent of liver extract over a period and make a reticulated count every other day; the reticulated red blood cells should show a steady increase up to the 7th or 9th day then begin to decline as the non reticulated red blood cells increase up to about 3,500,000 with a reticulated count at this stage of 2 or 3%. This phenomenon, when occurring, proves the potency of the liver extract and the diagnosis. If it does not occur the diagnosis is in error or the liver extract is not potent.

Anuria.—In anuria we have a cessation of renal function.

Cholera.—The disease in which anuria is most characteristic is cholera. During the stage of evacuation the urinary secretion becomes less and less, there is along with the progressive failure of circulation and, during the algid stage, a suppression of urine. The anuria seems to run parallel with an acidosis and intravenous injections of bicarbonate of soda solutions tend to prevent anuria. In the stage of reaction the favorable outcome is the reappearance of urine, which increases in amount to become a polyuria. In unfavorable cases the anuria continues.

Beriberi.—In dropsical beriberi there is an oliguria or, rarely, an anuria which with the rapid disappearance of the general body oedema may become an excessive polyuria.

Blackwater Fever.—In blackwater fever anuria may result from the blocking up of the renal tubules by haemoglobin casts. Acidosis is present and alkaline treatment is then indicated. The urine is irritating so that there is vesical tenesmus with frequent urination.

Heat Stroke.—Oliguria or anuria is common and may be followed, during convalescence, by a polyuria. Marked irritation of the bladder, associated with suppression of sweating, may be indicative of oncoming heat stroke.

Yellow Fever.—The degree of renal involvement is of great prognostic value in yellow fever, and those cases where the oliguria goes on to suppression are apt to terminate fatally.

Ascites.—An accumulation of fluid in the peritoneal cavity. The causes of ascites in the order of their frequency are: (1) Cardiac failure. (2) Renal disease. (3) Cirrhosis of the liver. (4) Tuberculous peritonitis. (5) Abdominal tumors, both malignant and benign. Other etiologic factors to be considered are intestinal obstruction, pericardial adhesions, pernicious anaemia, visceral syphilis, thrombosis of the inferior vena cava, tumors of kidney, perisplenitis, perihepatitis, peritoneal adhesions, hookworm disease, echinococcus disease, eclampsia, ovarian cysts and tumors.

In cardiac failure, cirrhosis of the liver, and renal failure the fluid frequently accumulates with great rapidity, with as much as thirty to fifty ounces daily. Tuberculous peritonitis as a rule shows a more gradual rate, possibly five or six ounces daily.

The diagnosis of ascites as a rule can be made on the presence of painless distention, moveable dullness, smooth shiny skin surface, broadening of the base of the thorax, obliteration or distention of the navel, enlargement of the superficial veins and fluctuation on palpation.

Some of the conditions which must be distinguished from ascites are: (1) Obesity of abdomen; in this condition there may actually be a percussion wave on tapping the flanks but there is no dullness in the flank. (2) Tympanites, no percussion wave, no changeable dullness and the X-ray findings serve to differentiate this condition. (3) Cysts, the enlargement due to cyst is frequently unilateral as in cyst involving the kidney or the ovary and it may be possible to outline the cyst and even move it about. (4) Choleperitoneum, due to rupture of bile duct or perforation of gall bladder; the history of the case, the occurrence of pain and a history of trauma or preceding gallstone

attack should differentiate. (5) Haemoperitoneum, blood in peritoneal cavity may be due to extra uterine pregnancy, rupture of a viscus, rupture of an abdominal aneurysm, rupture of varicose veins, and also may be due to carcinoma or sarcoma. The patient shows pallor, dyspnoea, collapse and immediate laparotomy is a necessity. (6) Distention of the bladder may also simulate ascites but the character of the tumor mass is pear shaped with retention of the tympanitic note in the flanks. This suggests a distended bladder which can be verified by catheterization. Chylous ascites due to rupture of the thoracic duct or of the receptaculum chyli may produce fluid in the peritoneal cavity. Filariasis may be a cause of chylous ascites. Added causes of ascites are; chronic anaemia, splenic anaemia, splenomyelogenous leukaemia, Pick's disease, pernicious anaemia and aplastic anaemia.

Beriberi.—See oedema and neuritis.

Blackwater Fever.—Haemoglobinuria, jaundice, enlarged spleen, early vomiting and history of malaria. The haemoglobinuric, port wine-colored urine, occurring in a patient previously ill with malaria is practically pathognomonic. Examine filtrate of urine spectroscopically for haemoglobin and methaemoglobin or by benzedine or orthotolidine test. Examine blood for malarial parasites and melaniferous leucocytes; blood serum for haemoglobin and bilirubin (Van den Bergh test), and for methaemalbumin by the spectroscopic test. Donath Landsteiner test negative.

Blood Pressure, low.—See hypotension.

Bone Affections.—The bones become soft in rickets and osteomalacia, brittle in general paresis, tabes dorsalis and in the senile. Malignancy must be considered when bone is invaded by a pathological process. Fungous infections (Actinomyces), syphilis, yaws and leprosy are common causes of bone affections.

Ainhum.—In this disease there is thinning or absorption of the bones of the toe. A fibrous cord replaces the bony structures.

Big Heel.—There has been observed in natives of the Gold Coast an affection of the os calcis somewhat like that involving the superior maxillary bones in goundou. The disease begins with pain and tenderness of one or both heels. The enlargement may involve only one os calcis or affect both bones. There is no joint involvement but locomotion is interfered with. There are periods of improvement which are followed by return of the pains.

Goundou.—In goundou the nasal bones and the nasal processes of the superior maxilla are the seat of symmetrical swellings of the nature of a hypertrophic osteitis. These exostoses may be quite large so that there is interference with vision. There is little or no pain connected with the bony growths and there is no invasive tendency.

Mycetoma.—As the result of the invasion of an extremity—usually the foot—with the causative fungi, disorganization of the tissues involved takes place. The granulomatous process invades muscles and bones and as a result of the sinus formation we have the bones converted into a softened, cheesy mass. This disintegration of bone and other tissues is attended with little or no pain. The granules discharging through the sinuses may suggest the proper diagnosis.

Bubo.—The enlargement of lymphatic glands accompanied by inflammatory changes and frequently by suppuration is most common in the groin and axilla. Venereal buboes generally occur in the groin as a result of gonorrhoea, chancroid or syphilis. Other causes of bubo in the groin are plague, rat bite fever, and possibly tularaemia. Climatic bubo is a form of tropical bubo due to a filtrable virus. Filariasis, in reality, does not cause a bubo as it is not accompanied by inflammatory changes, unless bacterial infection results. The different forms of bubo must be differentiated by microscopical and bacteriological examinations.

Chill.—Clinically a true chill or rigor consists of a shivering, shaking or sudden tremor of the voluntary muscles of varying duration, accompanied by sensations of cold and often accompanied or followed by an elevation of temperature. A definite chill followed by an elevation of temperature in a previously healthy person is generally indicative of systemic disease. It is in cases of recurring chills that this symptom is of definite value in differential diagnosis. The occurrence of an initial chill may give much needed information when correlated with the clinical findings. Biliary colic may lead to

repeated attacks of rigors and a chill may follow catheterization without infection. Sepsis, peritonitis, osteomyelitis, and erysipelas as a rule have an initial chill. Protein shock is a common cause of chill.

Cabot states that chills without any abnormal physical signs and with a normal blood picture are most often due to sepsis in the kidney, liver, or bile ducts.

Diseases with Recurring Chill

Leishmaniasis.—Indefinite onset, possibly daily chill, remittent fever, with a double rise in 24 hours. This double rise is characteristic and assists in differentiating typhoid and undulant fever.

Malaria.—The paroxysm of benign tertian usually commences with malaise and a slight headache followed by chilly sensations radiating from the spinal column to the extremities which give way to actual chill with shaking of body and chattering of teeth, pinched face, cyanosis, and cutis anserina. If the rectal temperature is taken it will be found that the fever has already begun, yet the patient desires wraps. As the chill subsides the face becomes flushed and blankets are cast aside and the elevation of temperature may be 104 or 105°F. This fever stage lasts from four to six hours and is followed by a sweating stage. The chills tend to recur at regular intervals, the time depending upon the type of organism. The finding of plasmodia in the blood confirms the diagnosis. In subtertian malaria there are often "blind chills."

Pyelitis, stone in the common duct and infective endocarditis may give rise to recurring chills, with intermittent or remittent fever.

Septicopyemia is characterized by recurrent chills without regularity. These may occur daily or every other day. The finding of foci of infection or local signs of emboli with a high leucocyte count and the blood negative for plasmodia should differentiate from malaria. Enlarged spleen is common in both conditions.

Diseases in Which Initial Chill Helps in Diagnosis

Initial chill with rapid rise in temperature is observed in rat bite fever, infectious jaundice, tularaemia and typhus fever.

Filariasis.—Elephantoid fever at times has sudden onset with rigors and high fever terminating with profuse sweating. Redness of legs or scrotum accompanied by lymphangitis and painful lymph glands should be sufficient to differentiate from malaria. Filarial infection is confirmed by finding of embryos in blood films. The possibility of this condition being an allergic manifestation has been mentioned. It is most likely a bacterial lymphangitis engrafted on the filariasis.

Pneumonia, Lobar.—In no disease is an initial chill so constant and severe and of such early diagnostic aid. Chill, fever, pain in side, cough, short, rapid respiration, flushed cheeks, blood-tinged, rusty, tenacious sputum is practically pathognomonic. This disease is a common cause of death in the tropics.

Spotted Fever of the Rocky Mountains.—Sudden onset with severe chill, slow rise of temperature, enlarged spleen, photophobia and joint pains. The typical eruption appears from second to fifth day of the disease and is an aid in diagnosis. Typhus often shows a more abrupt rise of temperature than Rocky Mountain fever. These two conditions show a marked resemblance and laboratory aid is necessary to differentiate.

Diseases in Which Certain Symptoms May Be Confused with Chill

Cholera.—Chill is uncommon but the surface temperature is low while that of the rectum may be 10° higher. Algid pernicious malaria may be confused with cholera but in malaria the axillary temperature is high and the diarrhoea is not so profuse.

Liver Abscess.—Shows an evening rise of temperature with sweating which is not preceded by a chill. Marked rigors are rare, but have been reported shortly before rupture. X-ray may be of value in differential diagnosis.

Cachexia.—Malnutrition with a marked state of general ill health is found following repeated attacks of malaria, and in hookworm disease, syphilis, pellagra, malignancy, and in the terminal stage of many diseases, as kala-azar. In the terminal stage of a disease it is of slight diagnostic value. Cachexia occurs fairly early in carcinoma of the

stomach and produces marked malnutrition with anaemia. In syphilis there is usually the history of infection and a positive blood serum reaction.

Ancylostomiasis.—Physical and mental retardation, little energy or initiative is a common complaint. The decrease in red blood cells may reach 2,000,000. Eosinophilia is characteristic and may reach 35%. This one finding alone should suggest an examination of faeces for ova or parasites. However, eosinophilia is usual in other helminthic infections.

Malaria.—History of repeated attacks, retinal haemorrhages, enlarged spleen, enlarged liver. Therapeutic test and the finding of the plasmodia in the blood are diagnostic. The cachexia of both hookworm disease and of malaria may show marked anaemia, swelling about the ankles, palpitation and shortness of breath. Finding of ova in faeces is diagnostic of the former. Eosinophilia is significant in hookworm infection and is not found in malaria.

Pellagra.—There is a wasting of all organs and tissues so that emaciation in this disease is marked. The localized, symmetrical, delimited, striking skin eruption or pigmentation is characteristic. History of previous gastrointestinal tract disturbances and the neurological manifestations should cause one to suspect pellagra.

Syphilis.—The history or presence of an initial lesion, anaemia, icteroid tinting of skin, positive Kahn reaction would suggest syphilis as the cause of the cachexia.

Other conditions to consider would be in the order named, dysentery, scurvy, chronic alcoholism, trichinosis, and cirrhosis of the liver.

Cholera.—This disease is characterized by state of evacuation collapse, cyanosis, pinched face, cold, clammy skin, diarrhoea, high red blood count, concentrated blood, low blood pressure. The difference between surface temperature and rectal temperature may be 10°F.

Laboratory Diagnosis.—(1) Recovery of cholera vibrio. (2) Agglutination tests. (3) Cholera red reaction.

Chyluria.—Vesical varices from lymphatic obstruction, due to filarial disease, are the most frequent cause of the milky urine of chyluria. The urine usually has a pinkish tinge from blood admixture so that the condition is really a haemato-chyluria. The thoracic duct may not be the seat of obstruction which has taken place elsewhere when the condition is lymphuria instead of chyluria. Lymph and chyle differ in fat content, the former having from very little to about 3% while the latter has 5% or more of emulsified fat. Chyle has also more than twice as much proteid as does lymph. In chyluria the morning urine is often clear while that at night is milky. On standing, chylous urine separates into an upper cream-like layer with a pinkish sediment and, between, a pinkish-white fluid in which floats a clot. Centrifuge the urine. Filarial embryos may or may not be found in the urine. Sometimes they are present in the blood.

Coma.—A loss of consciousness from which the patient cannot be aroused may be be due to alcohol, apoplexy, diabetes, pernicious malaria, uraemia, poisoning by certain drugs, sunstroke, and eclampsia. See delirium and coma.

Convulsions.—Paraxysms of generalized muscular contractions may occur in tetany, rickets, alcoholism, arsenic poisoning, tetanus, epilepsy, meningitis, heat stroke, brain lesions and eclampsia. In children, especially in scorpion poisoning.

Cramps.—A painful involuntary muscular contraction may follow over-exertion and is a common phenomenon in athletes; also it is a prominent feature of cholera.

Heat Exhaustion.—Severe muscle cramps of leg and abdomen occur. See delirium and coma.

Tetany.—It is in this condition that cramps are so characteristic and diagnostic; the fingers are flexed at metacarpal joints and terminal phalanges rigidly extended while the thumb is flexed across the palm. The wrists and elbows are flexed and arms held rigidly across chest. The feet turned in and the foot arched. This position is practically diagnostic. (Martin's sign).

Cyanosis.—Blueness of the skin, or purplish to blue tint of the face is a common symptom of cardiac failure, acute alcoholism, asthma, asphyxia of drowning, erythraemia with sclerosis of the pumonary artery (Ayerza's disease), carbon monoxide poisoning, foreign bodies in the air passages, apoplexy, tetanus and tetany.

Cholera.—As cyanosis develops the red count goes up even to 8,000,000 with a corresponding or greater increase in the leucocyte count. The estimation of the low blood pressure is important as indicating the necessity for intravenous injections. The determination of the degree of serum acidosis is also indicated with reference to alkaline treatment. In a convalescent from a disease suspected as cholera an agglutination test would be of value, and in the absence of the serum of immunized animals one could use that of a cholera convalescent against a spirillum isolated from the stool of a suspected case of cholera. Films from flecks in rice-water stools usually show many vibrios with "fish-in-stream" appearance. Identify by culture and agglutination test with cholera immune serum.

Plasmochin.—The most important toxic manifestation of plasmochin is cyanosis without dyspnoea. A methaemoglobinaemia results and cases have been reported when the symptoms were much like those of blackwater fever with methaemoglobinuria, jaundice, and very great red cell destruction.

Death, Sudden, Causes of.—Coronary occlusion, angina pectoris, cerebral haemorrhage, rupture of aneurysm, sunstroke, shock, diabetic coma, uraemia, valvular disease of the heart, especially aortic, and rupture of a viscus. Sudden emotional trauma may result in death.

Diarrhoea.—Frequency of defecation is not necessarily diarrhoea. The essential factor in diarrhoea is the abnormally rapid passage of food residue through the alimentary canal accompanied by fluid stools. An acute onset suggests a toxic or infective origin while a gradual onset in a middle aged individual, suggests new growth. Diarrhoea may be due to mechanical or chemical stimulation of gastric motor activity. Nervous, fermentative, fatty, chylous, and putrefactive diarrhoeas are recognised. Sprue or new growths may originate diarrhoeas. See dysentery. The chronic diarrhoeas of the tropics are often associated with amoebic dysentery and in such cases we generally get a history of recurring attacks of diarrhoea separated by periods of constipation.

In sprue the condition generally sets in as a morning diarrhoea, very profuse and painless. Hill diarrhoea also shows frequent stools of whitish color from early morning until about noon. The typical stool of sprue is a gas-permeated, putty-colored, offensive mass, extraordinarily copious.

In cholera the rice-water stool, which is not attended by pain, causes an unusual sense of prostration even at the onset of the stage of evacuation.

In pellagra we often have a recurring diarrhoea or mild manifestations of dysentery. The stool of pellagra is darker and less copious than that of sprue and shows only a normal fat content while that of sprue is very fatty—as much as 30% of ingested fat may appear in the sprue stool as against about 5% for the normal one.

In Japanese schistosomiasis, or Katayama disease, following the stage of urticarial fever, the microscopical examination of the blood-tinged bit of mucus (which often caps the stool) for the spineless ova of the fluke is the most favorable measure for determining the diagnosis. The diarrhoea may be intermittent.

The fluke diseases of the liver and intestines give rise to various disturbances. The diagnosis is made by finding the specific ova in the stools.

In infections with *Strongyloides stercoralis* there may be vague manifestations of neurasthenia and diarrhoeal disturbances. Cochin China diarrhoea was in earlier years regarded as a *Strongyloides* infection and this parasite is often found in diarrhoeal cases in that country and elsewhere in the world.

Intestinal flagellates are so common in the stools of well people in the tropics that one should be very careful in assigning a pathogenic rôle to them. It is now accepted by many that *Giardia lamblia* can bring about exhausting diarrhoea.

After the repeated examination of the faeces without finding ova or parasites one should think of tuberculosis, syphilis, ulcerative colitis, and such other causes of diarrhoea as sprue and pellagra.

Tetany.—The calcium of the body is utilized to combine with fatty acids to form calcium soap in chylous and fatty diarrhoea, thereby diminishing the blood calcium and tetany results. Scott having found a deficiency of the calcium in the blood in sprue has suggested giiving calcium and parathyroid in this disease.

Delirium and Coma.—It is difficult to make a sharp distinction between a disease showing delirium and one showing coma as delirious states tend to be followed by coma or such conditions may alternate.

Cholera.—Following upon the algid stage of cholera we may have a stage of reaction without the reappearance of the urine, in which a typhoid state, with low muttering delirium or even with an acute delirious state, supervenes.

Dysentery.—In very toxic cases of bacillary dysentery there may be a mild delirium.

Heat Stroke.—There may be no more difficult problem encountered in the tropics than the one of differentiating cerebral malaria from heat stroke. In heat stroke we may have either delirium or coma.

Malaria.—In the ordinary paroxysm of malignant tertian there is quite a tendency to flightiness during the prolonged hot stage. In the cerebral types of pernicious malaria there may be violent delirium followed by coma or the patient may be comatose from the onset of the paroxysm. Such conditions are often mistaken for sun stroke. In the comatose form of malaria we have a high temperature with sighing or stertorous breathing and at times Cheyne-Stokes respiration.

Oroya Fever.—Delirium is often noted. Marked anaemia irregular fever, pain in the bones, enlarged spleen and delirium should make one think of Oroya fever but the diagnosis can be definitely made only by the blood examination and the finding of *Bartonella* in the red corpuscles.

Pellagra.—Comatose states following upon the acute confusional psychoses of pellagra are not uncommon. Pellagra may show an acute collapse delirium.

Plague.—In plague there is more of a mild delirious state in which the patient has a great tendency to wander about. The mental state is rather that of an intoxicated person with the thickness of speech and retardation of mental processes.

Rat Bite Fever.—Delirium is a common finding in rat bite fever.

Spotted Fever of the Rocky Mountains tends to produce stuporous states.

Trypanosomiasis.—Toward the end of the sleeping sickness stage we have a subnormal temperature with a comatose state.

Tsutsugamushi.—A delirious state, especially at night, is often noted in tsutsugamushi.

Typhus Fever.—In typhus fever (tabardillo) delirious or stuporous states are to be expected about the end of the first week or even earlier. This is a disease in which the clouding of the consciousness is almost as marked as in plague. Delirium is more apt to occur at night.

In the above *infections*, the origin of the delirium or coma is determined by the discovery of the specific organism. In pellagra, the nervous and mental symptoms associated with the cutaneous lesions are often of assistance in diagnosis, while in spotted fever, tsutsugamushi and typhus fever the Weil-felix reaction may be of value in diagnosis. (See p. 945.)

Yellow Fever.—In yellow fever the alert, suspicious mental state may give way to one of marked delirium requiring close watching to prevent the patient throwing himself from his bed. (See p. 898 for diagnosis.)

Dengue.—See temperature.

Dysentery.—The designation dysentery refers to a symptom complex. (1) Small, frequently passed mucous or muco-sanguinolent stools. (2) Pain, connected with spasm of the sphincter ani (tenesmus) and intestinal griping (tormina). The condition may be set up by different causes but bacillary and amoebic dysentery so outweigh the other causes that they should immediately be thought of when the term is used. See diarrhoea.

Amoebic Dysentery.—Diagnosis: (1) Examine stool for *Endamoeba histolytica.* (2) Study of cellular exudate from stool will help differentiate bacillary dysentery. (3) Usually no fever or toxaemia in amoebic dysentery.

Bacillary Dysentery.—This disease is characterized by: (1) Frequent, scanty stools of muco-purulent or muco-sanguinolent character. (2) Marked toxaemia and exhaustion. (3) Elevation of temperature 101 to 103°F. Diagnosis should be confirmed by isolation of the dysentery bacilli. See p. 568.

In *cholera* we have a profuse diarrhoea of rice water stools without colic or tenesmus.

Laboratory Aid.—Culture from stool; examination of cellular exudate is characteristic and will differentiate bacillary from amoebic dysentery. Tuberculosis cancerous and syphilitic processes as well as helminthic and other protozoal infections should be considered.

Dyspnoea.—Difficult or labored breathing may be expiratory or inspiratory and may be due to cardiac, renal, acidotic, or other causes. In dyspnoea the accessory muscles of respiration are often brought into play and in marked dyspnoea the alae nasae dilate and contract with each respiratory effort.

The common causes of dyspnoea are: Tuberculosis, pneumonia, cardiac decompensation, asthma, acidosis (diabetes mellitus), anaemia, pulmonary congestion, tumors and aneurysm.

Tropical conditions causing dyspnoea are: Typhoid, trichinosis, tetany, tetanus, rickets, scurvy, glanders, beriberi, pneumonic plague, and allergic manifestations.

It should be kept in mind that in cardiac dyspnoea the work of the heart is lessened when the patient is propped up or even leaning forward; which phenomenon may be of diagnostic value.

Eosinophilia.—Normally eosinophiles average about 2% (0.5 to 3%) of the white cell count. These cells rarely increase in number in infectious diseases or in those diseases terminating fatally. It is in the non bacterial type of disease that an eosinophilia occurs. Eosinophilia occurs following foreign protein injections and in conditions due to protein hypersensitiveness, such as hay fever, asthma, angioneurotic oedema and urticaria. It is also a characteristic blood cellular constituent in trichinosis, mycotic and various helminthological infections. According to Ehrlich and Lazarus eosinophiles are formed in the bone marrow and from there are attracted to the blood and other tissues, by the action of some toxin or other substance that is chemotactic for this cell. Their clinical significance is still debatable. The proportion of eosinophiles in the blood of children is greater than in that of adults. Where the eosinophiles are increased to 5%, we have a moderate eosinophilia. In some cases of infection with intestinal parasites, especially hookworms, but also from other parasites, as round and whip-worms, we may have an eosinophilia of 30 to 50%. In Guam, among the natives, it is difficult to find an eosinophile count under 15%. The eosinophilia tends to disappear when the anaemia becomes very severe. An increase of eosinophiles always attracts attention to the possibility of intestinal parasite infections or to skin affections. Eosinophilia is common in onchocerciasis and frequently occurs in *Loa* infections with Calabar swellings and in *Dracunculus* infection. The explanation of eosinophilia is obscure although Neisser regards the increased production of eosinophiles as an expression of sympathetic system irritation. The subject is discussed further in Filariasis, p. 1378.

Asthma.—According to Huber and Koessler (1922) eosinophilia is the most striking cellular constituent in the atopic (inherited) forms of asthma. In bacterial or infectious types, eosinophile cells were usually absent.

Hay Fever.—During the active symptoms of this condition eosinophiles may show an increase to 15%; prior to the advent of symptoms of hay fever, patients do not show an increase of eosinophiles in the blood. Sternberg (1928) states that the shock of the sudden entrance of a large amount of pollen protein into the circulation is probably the cause of the eosinophile increase.

Helminthological Infections.—In the earlier stages of ancylostomiasis and schistosomiasis we have a rather notable increase in the percentage of eosinophiles but with the advanced stages of these infections, with severe anaemia, the eosinophiles may even be absent. One should always keep in mind the very characteristic and marked eosinophilia of trichinosis when such a blood finding is encountered. There is often a leucocytosis of 15,000 to 20,000 in this disease. In the urticarial fever stage of Japanese schistosomiasis the marked eosinophilia is of great assistance in diagnosis One trouble about attaching importance to eosinophilia in the tropics is the confusion which is difficult to eliminate and which arises from infections with the more common but less important group of intestinal parasites such as *Ascaris* and *Trichuris* and some of the filariidae. *Echinococcus* infection has an eosinophilia which disappears when the

cyst is removed. Continuance of the eosinophilia indicates that all cysts were not gotten rid of.

Myelogenous Leukaemia.—Increase of both eosinophiles and mast cells is found in myelogenous leukaemia.

An eosinophilia tends to appear following splenectomy. With a Wright stain showing acid tendencies one may regard and count polymorphonuclears as eosinophiles unless noting smaller size of granules.

Skin Affections.—Eczema and psoriasis are not apt to give more than 3 or 4% eosinophiles. A rather high degree of eosinophilia is found in mycosis fungoides. Scabies also gives rise to an eosinophilia.

Trichinosis.—A combination of eosinophilia with fever and marked pains in the muscles is characteristic of this condition. This combination of symptoms would justify the excision of a piece of muscle for examination for encysted embryos.

Typhoid.—A normal or increased percentage of eosinophiles is strong evidence against a diagnosis of typhoid.

Eruptions.—The tropical fevers in which a more or less diagnostic exanthem may be noted are: African trypanosomiasis, rat bite fever, yaws, dengue, tsutsugamushi, spotted fever of the Rocky Mountains, typhus fever and trench fever.

Eye, Diagnostic Information Obtained from. *Ancylostomiasis.*—Retinal haemorrhages may occur with marked hookworm anaemia. Stiles notes a fixed stare in hookworm cases, the eye itself somewhat resembling the eye of a fish. Among other diseases showing ocular manifestations may be mentioned one associated with fibrous nodules in the upper lid due to a larval dibothriocephalid, *Sparganum mansoni.*

In pericorneal conjunctivitis, the microfilariae of *Onchocerca* are usually found in a snip of the conjunctiva.

Aneurysm.—Inequality of pupil is a common finding through stimulation of sympathetic nerve supply to the corresponding pupil.

Arsenic Poisoning.—Puffiness of lids is a common finding

Bacillary Dysentery.—Quite a number of cases have been reported where along with an arthritic complication there has been conjunctivitis. In 6 cases of dysenteric conjunctivitis, Maxwell noted that 4 cases had arthritis and 3 of the latter showed anterior uveitis. The conjunctivitis lasted about a week. Relapses seem liable to occur. In none of the cases has there been recovered from the conjunctival secretion the organism of dysentery.

Beriberi.—In this disease there have been reported the following eye complications: (1) Retrobulbar neuritis. (2) Paralyses of the muscles of the eye. (3) Decreased sensibility of the cornea and conjunctiva.

Botulism.—Diplopia and ocular paralysis are common findings.

Cataract.—The general impression is that cataract is more frequent in the tropical regions than in Europe and as bearing out this view Elliott notes that cataract among those Europeans who have served in India seems more frequent than among those who have remained in England. Cataract is also more common in the southern part of China than in the northern portion.

Cholera.—As a result of the loss of body fluids the lachrymal secretion is scanty or absent and we have various conjunctival and corneal troubles unless the eye is frequently irrigated with normal saline. Vitreous opacities and cataract may follow cholera.

Diabetes.—In diabetic coma the soft eye ball may be of great diagnostic aid and is regarded as a characteristic sign of this condition. Cataract is common and when encountered before the age of fifty diabetes must be excluded.

Diphtheria.—Neuritis of the oculo-motor nerve producing ptosis or squint, or more commonly paralysis of ciliary muscle may follow diphtheria.

Encephalitis Lethargica.—Transient double vision and paralysis of one of the ocular muscles occurs especially at the onset of the disease and may be of only a few hours duration.

Endocarditis, Subacute.—Petechial subconjunctival haemorrhages may suggest this condition.

Exophthalmic Goiter —Lid-lag and bilateral exophthalmos are cardinal signs of this disease.

Filariasis.—In that filarial infection caused by *Loa loa*, at one time designated *Filaria oculi*, there seems a special tendency for the adult worms to wander to the subcutaneous tissues in the neighborhood of the eyes or under the palpebral or ocular conjunctivae. When moving under the conjunctiva the worms cause marked irritation and at times pain. There may be considerable swelling so that the patient cannot for a time see out of the invaded eye. It has been stated that the worms may enter the anterior chamber of the eye but this is questionable. Lesions of the cornea and iris may result from the migrations through the body of the microfilariae of *Onchocerca volvulus*. Keratitis punctata and iritis have frequently been observed in *O. caecutiens* infections in Guatemala and Africa. For other helminthic infections of the eye, see p. 1371.

Glare Asthenopia and Glare Conjunctivitis.—These manifestations of tropical sunlight vary in different individuals. From slight discomfort, after being exposed to bright sunlight, the condition may grow worse until there is severe headache and pain and tenderness of the eyeballs. So hyperaesthetic may these individuals become that even bright moonlight may cause discomfort. The fundus is normal, but one should have in mind the suffering which an ophthalmoscopic examination may cause. The pupils should not be dilated. It is wise always to wear tinted glasses when in the sun, particularly if one experiences discomfort. While there may be little incapacity at first, the discomfort may after a few months or years of tropical residence become so marked as to necessitate one's leaving the tropics. No other kind of glass to obviate the ill effects of glare equals the Crooke's glass. Cases of glare asthenopia often show conjunctivitis and in some cases this is extreme. There is often a combination of wind, dust and glare producing the conjunctivitis. These factors with the course of the tears extending inward influence the frequency of pinguecula and pterygium in the tropics.

Infectious Jaundice.—Intense injection of the eyes may constitute the earliest and most striking feature. By some, the injection of the conjunctivae is regarded as almost pathognomonic, presenting a distinct network of vessels in the cornea and sclerotics.

Leprosy.—The eye is more frequently involved in nodular than in nerve leprosy. In the former we have infiltration of the conjunctiva which may extend to the cornea. The leprous nodules invading the palpebral conjunctiva tend to ulcerate and bring about various distortions of the eyelids, producing ectropion. Iritis, iridocyclitis and iridochoroiditis are less frequent than conjunctivitis and keratitis. The optic nerve and the retina are only rarely involved. In nerve leprosy the eye changes are chiefly connected with the lesions of the fifth and facial nerves. Ptosis and paralytic ectropion occur with frequency. Ophthalmia and corneal ulcerations may lead to total destruction of the eye. The cornea may be anaesthetic. Paralysis of one or more ocular muscles may cause squint or diplopia.

Malaria.—It is questionable whether the forms of conjunctivitis and keratitis at times reported as due to malarial infection are not rather of other origin. Iritis is rarely a complication of malaria. Retinal haemorrhages may occur in malarial cachexia and cerebral types of pernicious malaria. Another rare malarial complication is amblyopia. In this there is an optic neuritis with rosy or grayish-red disc and the loss of vision is not complete, while in quinine amblyopia the disc is white and the vision completely lost for a time.

Meningitis.—Ocular paralysis may accompany other signs of this disease.

Multiple Sclerosis.—Transient unilateral occular paralysis or transient blindness may be an early sign of multiple sclerosis. This disease frequently simulates hysteria. Nystagmus, intention tremor and scanning speech are characteristic.

Myxoedema.—Loss of the outer third of the eyebrow frequently occurs.

Nephritis.—Puffiness of eye lid is frequently associated with nephritis. Defective vision is common in chronic nephritis and may be the first subjective symptom. The eye grounds in chronic nephritis are almost pathognomonic, flame shaped haemorrhages with white spots or radiating lines in the region of the macula.

Night Blindness and Xerophthalmia.—Both of these conditions are quite common in certain parts of the tropics and the view that the heat of the tropics and the tropical sunlight were potent factors had precedence until our study of vitamin requirements

showed the etiology to rest in deficiency of fat soluble A. It is now known that cod-liver oil is particularly rich in this vitamin and that in this agent we have our best preventive and curative agent for these eye conditions. It is well known that rats fed on a diet deficient in fat soluble A develop xerophthalmia. Night blindness (nyctalopia) is best known among the crews of sailing ships, especially when becalmed in tropical waters, and some influence of sunlight was considered the cause, but we now know that it is among such personnel that ship beriberi and scurvy are prone to occur by reason of deficiencies in water soluble B and the antiscorbutic vitamins. In such a dietary fat soluble A would also probably be lacking.

Pappataci Fever.—Injection of conjunctiva is marked, often in band formation extending across eye ball. Eye is tender to pressure and photophobia is severe.

Santonin.—This drug produces yellow vision.

Sclera, Jaundice of.—This finding may suggest obstruction of common duct, sclerosis of the liver, gall stones, carcinoma of the head of the pancreas, catarrhal jaundice, acute yellow atrophy, haemolytic jaundice, pernicious anaemia, sickle cell anaemia, yellow fever, malaria, black water fever, *Weil's disease* and poisoning by arsenic, phosphorus and carbon tetrachloride.

Syphilis.—Uneven loss of eyebrow suggests late secondary syphilis particularly if accompanied by irregular loss of hair over temporal regions. Corneal scarring may evidence a previous syphilitic keratitis. Inequality, irregularity of pupil and diminished or absent light reflex should make one suspect syphilis. Bilateral interstitial keratitis indicates congenital syphilis. Diplopia, ptosis, or paralysis of any muscle of the eye suggests syphilis as the most common cause.

Tick Fever.—In the relapsing fever of South Africa iritis has been noted as occasionally occurring.

Tularaemia.—In the oculoglandular type of the disease we have a primary localization in the conjunctival sac. There is weeping, swelling of the lids and oedema of the ocular conjunctiva and papule formation on lower lid. Tenderness and pain in preauricular, parotid, submaxillary or anterior cervical lymph glands when present are most suggestive.

Trypanosomiasis.—Eye lesions are quite frequent in this disease, these being keratitis, iridocyclitis or conjunctivitis. Oedema about the eyes is of importance in diagnosis. Eye lesions have been reported as more common in Rhodesian trypanosomiasis. The atoxyl and tryparasmide treatment of the disease may cause optic neuritis and blindness.

Yellow Fever.—In the period of onset a feature of the so-called "facies" of the disease may be marked injection of the conjunctivae with sensitiveness to light. Rush likened it to the eye of a wild animal as contrasted with the less ferocious eye of bilious remittent fever which more resembled that of a domesticated animal. About the third or fourth day the earliest manifestation of jaundice presents itself in the ocular conjunctivae.

Face.—Puffiness of the face with enlarged thyroid has sometimes been reported in acute types of American trypanosomiasis. Such cases may have been associated with endemic thyroid disease. One should also consider glomerulo-nephritis and myxoedema with this symptom.

Faeces.—It is advisable to examine a stool macroscopically before taking up the microscopical examination. Pus or blood in stools may often be noted without the aid of the microscope. The normal stool is sausage-shaped and soft. In obstruction of the common bile duct we have acholic, whitish, foul-smelling stools. If the putty color be due to bacterial change exposure to the air will restore the brownish tinge.

Cholera.—The faecal character of the stool in cholera is soon lost and the typical rice-water stool takes its place. This designation is very apt and the flocculi of intestinal epithelium, in a watery, slightly opaque fluid, suggests rice-water.

Dysentery.—The muco-purulent stool of bacillary dysentery is flecked or streaked with blood or a very bright blood-tinged mucus, rather than the homogeneous grayish brown, gelatinous mixture or disintegrated blood and mucus of the amoebic stool.

The mucus of bacillary dysentery is opaque and grayish from the great number of pus and phagocytic cells. It is well to remember that Charcot-Leyden crystals,

which are practically always absent from bacillary dysentery stools, are not infrequent findings in the amoebae-containing stools; of course, these crystals appear in other intestinal parasite infections.

Sprue.—The diarrhoeal movements are remarkably copious and soon change from bile coloured, liquid evacuations to the characteristic putty-colored, pultaceous, gas bubble permeated, offensive stool of sprue. The sprue stool shows an increase in fats, chiefly fatty acids.

Faget's Sign.—A falling pulse rate with constant temperature, or a constant pulse rate with a rising temperature. This sign is of value in diagnosis of yellow fever.

Fever.—Probably the most reliable clinical sign of the existance of a pathological condition is a rise in body temperature above normal. The results of the introduction into the body of bacteria or bacterial toxins are evidenced by fever. The relationship of fever to organismal invasion is best shown in malaria where the fever corresponds to the different types of organisms present in the blood stream. Diagnostic data obtained from the study of the type of fever present, are considered under "temperature."

Filariasis.—See eosinophilia, glands and skin. Diagnosis confirmed by finding microfilariae in blood or by puncture of the lymphatic lesions.

Gait.—The manner or style of walking may give valuable aid in the diagnosis of affections of the nervous system, especially syphilis, yaws, diphtheria, poliomyelitis, Parkinson's disease and neuritis resulting from alcohol and other poisons. There are no gaits which can, strictly speaking, be regarded as peculiar to any tropical disease

Beriberi.—It is true that beriberi patients show the steppage gait of multiple neuritis as, owing to more or less foot-drop and lack of power to extend the toes, the patient lifts his foot high from the ground to avoid scraping the toes, and bends to the other side. It is as if the man were walking through a mire. Also striking is the manner in which a case of the paraplegic type of beriberi uses a stick held by his hands to assist him in dragging along his atrophied and enfeebled legs. The legs are widely separated and the stick placed in front makes the two legs and stick resemble a tripod. When other groups of muscles than the foot extensor ones become involved the gait is that of extreme weakness—a shuffling one.

Dengue.—We often note under dengue the designation dandyfied gait. This refers to the stilted, mincing gait of a dandy and is probably the explanation of the derivation of the word dengue. The pains about the site of the insertions of muscles with the slightest movement make these patients walk in a stiff, self-conscious manner.

Pellagra.—In pellagra we may see a gait in which the patient separates his legs rather widely and uses a stick in front, shuffling his feet along with knees slightly bent and soles of the feet scarcely raised from the ground. Some cases show a typical spastic paralytic gait.

Trypanosomiasis.—In sleeping sickness there is often a shuffling gait which is very striking. Sometimes it is as if one were dragging the feet along from pure muscular weakness.

Genito-urinary Organs.—Symptoms referable to the genito-urinary organs may vary greatly in nature from the pathognomonic lymph scrotum of filiariasis to an orchitis due to undulant fever. In puzzling febrile cases in the tropics one should always think of a possible pyelitis. Renal tuberculosis should also be kept in mind.

Ancylostomiasis.—In hook-worm disease menstruation is markedly interfered with and amenorrhoea is often a prominent symptom. Young men who have been affected before puberty show lack of development of pubic hair along with infantile genital organs. The girls do not show normal breast development.

Bilharziasis (Schistosomiasis).—The kidneys may be involved secondarily—the change being brought about by stone in the bladder and cystitis leading to hydronephrosis and pyelonephritis.

Blackwater Fever.—In blackwater fever there is usually marked pain in the region of the kidneys due to the plugging of the tubules with haemoglobin casts. Vesical tenesmus and pain along the ureters may also be present.

Cholera.—In this disease the kidneys are markedly affected, especially the epithelial lining of the tubules though such changes are usually transitory. (See p. 613.)

Cystitis.—Cases of cystitis occurring in dysentery have been reported which showed amoebae in the sediment of the urine. Such cases probably were connected with recto-vesical fistulae caused by amoebic ulceration.

Filariasis.—One of the manifestations of filarial disease is lymph scrotum in which the scrotum is covered with small blebs containing a chylous fluid which may possibly contain microfilariae. It is associated with recurring attacks of lymphangitis. There is also a filarial orchitis and we may have a lymphangitis of the lymphatics of the cord. Again filarial disease may show a chylocele in which the tunica vaginalis contains a fluid similar to that seen in the varices of lymph scrotum. This fluid may also show filarial embryos.

Funiculitis.—In endemic funiculitis there is a sudden onset with high temperature and pain in spermatic cord and epididymis. The general condition rapidly becomes grave with a hard, tender, cylindrical swelling along the cord and also pain and swelling of the epididymis. It is a streptococcus infection usually engrafted on a filarial or bilharzial process and demands immediate surgical measures.

Gangrene.—Cases of gangrene of the scrotum have been reported as connected with malaria. Gangrene of the scrotum and penis is not infrequently noted in Rocky Mountain fever.

Granuloma.—Granuloma of the pudenda is a disease which is common in many tropical countries and in the southern United States and in which organisms described as "Donovan's bodies" (perhaps related to *Bacillus mucous capsulatus*) may be demonstrated by microscopical examination.

Kala-azar may be accompanied by sloughing of the scrotum at the time manifestations of cancrum oris are noted.

Leprosy.—If leprosy comes on before puberty the sexual organs remain in an undeveloped condition. Leprous infiltrations are noted in the testicles and ovaries. In nerve leprosy, which does not usually come on until after puberty, the women may bear healthy children and it is now thought that the view that leprosy markedly tends to produce sterility is lacking in confirmation.

Malaria.—In malaria Thayer stated that nephritis occurred in about 2% of malignant tertian cases. MacFie, Lambers (1940) have called attention to the frequent occurrence of toxic nephritis in severe quartan infections. Boyd and Proske (1941) point out that malaria infection produces a nephrosis rather than a nephritis.

Orchitis.—Malta or undulant fever may rarely be attended by an orchitis.

Trichophyton Infection.—Dhobie itch is characteristically located in the crotch region.

Glands, Enlarged.—*Axillary.*—The arm is drained by a chain of the axillary lymphatics surrounding the axillary vessels. The anterior chest to the nipple is drained by a second axillary chain situated along the lower border of the pectoralis major. A third chain receives the lymphatics draining the posterior chest. The axillary lymph glands may become enlarged due to tularaemia, rat bite fever, plague, syphilis, infected wounds, Hodgkins disease, leukaemia, glandular fever and malignancy.

Cervical.—The lower lip, chin and floor of mouth are drained by the submental lymph glands. The submaxillary, beneath the mandible in the submaxillary triangle drain the face, lips, nose and gums. The ear and anterior scalp are drained by the superficial cervical. The posterior region is drained by the superficial occipital lymph glands. The posterior auricular nodes situated on the mastoid process are an important group. It is well to keep in mind both the superficial and the deep groups of cervical lymphatics when ascertaining the location of infection. The common causes of cervical lymphadenopathy are tonsillitis (glands below angle of jaw involved), tooth infection (glands at angle of jaw), scarlet fever, measles, tuberculosis, syphilis and glandular fever. The less common causes are Hodgkins disease and malignancy.

Inguinal.—The external genitals, the lower part of the abdomen and back, the buttocks, and the anus are drained by the inguinal group of lymphatic glands lying about Poupart's ligament, while the femoral group lying below the saphenous opening drain the leg. The inguinal group may become enlarged due to chancre, chancroid and gonorrhoea. Tropical diseases causing enlargement are bubonic plague, filariasis, climatic bubo and sometimes tularaemia. In bubonic plague the femoral glands are more frequently enlarged than those above Poupart's ligament.

Tropical diseases causing general lymphadenopathy are glanders, tularemia, filariasis, undulant fever, bubonic plague, trypanosomiasis, rat bite fever, leprosy, yaws and American leishmaniasis.

American Leishmaniasis.—Not only is there often enlargement of the lymphatic glands but likewise we may have lymphangitis lines leading from the ulcer to the glands. The glands may be large and painful and may remain enlarged after the recovery of the patient.

American and African Trypanosomiasis may also show lymphatic enlargement. Enlargement of the thyroid was formerly reported, but this is now regarded as an independent condition.

Climatic Bubo.—The onset is gradual often accompanied by a low remittent type of fever. The primary lesion is sometimes detectable on the prepuce or male genitalia. The glands are only slightly tender and have sometimes been called fatigue glands as they produce a feeling of weariness after even moderate exercise. The inguinal glands of one or both sides are the ones involved and the overlying skin does not show the redness of a chancroidal or gonorrhoeal bubo. There is often a softening in the center of the affected glands.

Dengue.—It is often stated that the superficial cervical glands are enlarged in dengue but not in dengue-like fevers. Stitt has not observed in the cases he has seen either constant or well marked glandular enlargements.

Filariasis.—Varicose groin glands are frequently associated with lymph scrotum, chylocele or chyluria. The glandular masses are soft and doughy. The consistency is often that of a lipoma. The overlying skin slips over the glandular mass. These glands are sometimes mistaken for inguinal hernia. They do not give a tympanitic note and disappear slowly upon firm pressure with the patient lying down but return even with the pressure maintained upon assuming the upright position. There is no impulse on coughing. If a sterile hypodermic needle be inserted into the mass a chylous fluid slowly and persistently comes out of the needle drop by drop and this material may show filarial embryos. *Onchocerca volvulus* also obstructs the lymphatics and may give rise to swellings of considerable size along the course of the lymphatics.

Leishmaniasis.—Kala-azar may or may not show enlargement of lymph glands. Films from excised lymph glands may show leishmania bodies. There may be general enlargement of the lymphatic glands which are rather hard, discrete and not bound down to the overlying skin. These glands may be somewhat tender or entirely painless.

Leprosy.—In leprosy the glands draining involved regions become enlarged but do not show a tendency to suppuration. The glands most frequently involved are the cervical and groin glands.

Pediculosis.—In pediculosis of the hairy scalp the scratching back of the neck may result in pus infection with enlargement of the tributary cervical glands.

Plague.—The buboes are the most characteristic feature of the more common form of plague, bubonic plague. There may also be slight enlargement and tenderness of the glands in septicaemic and pneumonic plague but many such cases fail to show any evidence of superficial glandular enlargement. In pestis minor the only feature suggestive of plague is the glandular enlargement. Very characteristic of the glandular involvement in plague is the marked tenderness of such glands. The slight pressure of palpation causes some pain and a sharp punch over an affected gland, excruciating pain. So exquisitely painful are these buboes that the patient with groin or axillary buboes will flex the leg or extend the arm to relieve pressure. In about 70% of cases the bubo is located in the groin, with 15% to 20% for axillary involvement and 5% to 10% for the submaxillary or cervical region. There may be involvement of both deep and superficial glands of a region, such buboes giving a large area of induration. As a rule there is a single bubo. The bubo is formed not only by the glands but by a periglandular oedema which fuses the glands into a solid mass. The buboes tend to suppurate about the commencement of the second week, so that gland puncture with subsequent culturing for plague bacilli and animal inoculation should be carried out before this time as pyogenic organisms may replace the plague bacilli upon suppuration taking place.

Rat Bite Fever.—Glandular enlargement in the glands tributary to the healed infecting bite of the rat is characteristic of rat bite fever.

Trypanosomiasis.—One of the characteristics of the disease recognized as diagnostic more than 100 years ago is enlargement of the glands of the posterior cervical triangle (Winterbottom's sign). One of the most valuable of methods diagnostic of trypanosomiasis is by gland puncture, the juice obtained therefrom being examined in films for trypanosomes or inoculated into a monkey or guinea pig. Brazilian trypanosomiasis also shows glandular involvement.

Tsutsugamushi.—The glands which drain the area in which is located the ulcer at the site of the bite of the Kedani mite show swelling and tenderness.

Tularaemia.—The axillary glands are most frequently involved due to the greater incidence of infections on the hands. The initial wound may or may not heal before systemic symptoms of disease occur, but the initial wound tends to suppurate at the onset of the systemic symptoms and this is a diagnostic point of importance. There is often previous history of handling or cleaning rabbits. Initial lesion; later, fever of sudden onset, followed by a chill, is characteristic.

Yaws.—In yaws there may be glandular enlargement. According to Finucane the cervical glands are often involved in Fiji children. These glands do not tend to break down.

Haematemesis.—The vomiting of blood has to be differentiated from haemoptysis. Having determined that the patient is vomiting blood the second step is to determine the cause. Common causes to be considered: (1) Vomiting of swallowed blood from (*a*) bleeding gums (*b*) epistaxis (*c*) haemoptysis. (2) Diseases of the oesophagus. (3) Diseases of the stomach; (*a*) ulcer (*b*) carcinoma (*c*) irritation from arsenic or antimony. (4) Diseases of the duodenom; (*a*) ulcer (*b*) carcinoma (*c*) ulcerations (5) diseases of the liver (cirrhosis). (6) Blood diseases; (*a*) purpura (*b*) scurvy (*c*) haemophilia (*d*) leukaemia (*e*) splenic anaemia (*f*) malarial cachexia (*g*) syphilis. (7) Arterial hypertension and nephritis. (8) Tropical diseases; (*a*) yellow fever (*b*) malaria (*c*) cholera (*d*) dengue (*e*) onyalai.

Cholera.—Vomiting, at first of the contents of the stomach and later of rice-water material streaked with blood is a distressing feature of cholera. The vomiting, purging, cramps and painful contractures of the legs, intense exhaustion and cadaveric appearance are diagnostic features of cholera.

Dengue.—Rarely the initial symptom is the vomiting of blood streaked material in dengue.

Malaria Cachexia.—This condition may be accompanied by severe haematemesis. See malaria for diagnosis.

Pellagra.—Gastric disturbances especially gastralgia, pyrosis and eructations may be accompanied by the vomiting of blood in pellagra.

Syphilis.—Visceral syphilis may be a cause of vomiting of blood.

Yellow Fever.—Nausea and vomiting are more common than in other fevers. The black vomit is one of the most striking features of the disease. Sometimes pure blood is thrown up from the stomach.

Haematuria.—The presence of blood in the urine calls for a careful examination of the genito-urinary system. Common causes of blood in the urine are renal tuberculosis, hypertension, stone in kidney, nephritis, tumor of the kidney and gonorrhoea. Among tropical diseases that which immediately suggests haematuria is vesical bilharziasis due to *S. haematobium.* The blood in the urine is in the form of red cells; it is a haematuria and not a haemoglobinuria. The passage of blood usually occurs at the end of micturition and it is either in the last few drops of urine or in the sediment obtained after centrifuging that we note the terminal spined eggs of *S. haematobium* which proves the diagnosis.

Red blood cells in the urine may also be noted in the haematochyluria of filarial disease.

When we have blood in the urine in yellow fever it is a haematuria and comes on about the same time as the black vomit and other haemorrhages resulting from degeneration of the endothelial linings of the blood capillaries, which only takes place about the third or fourth day of the disease.

Haematuria may also be noted in plague at the time when the haemorrhages into the skin occur.

Haemoglobinuria.—The presence of haemoglobin in the urine occasionally occurs following extensive burns, poison from snake venom, administration of foreign sera or—most commonly—syphilis. The vast majority of cases of true tropical haemoglobinuria, however, are due either to blackwater fever or to the administration of the acid salts of quinine to one predisposed to quinine haemoglobinuria. While it must be admitted that haemoglobinuria may result from quinine it is certainly so rare in subtropical countries, where great amounts of quinine are administered in treatment of malaria, as to be unimportant. It is only where the malignant tertian parasite flourishes that we have the question of the importance of quinine in producing haemoglobinuria brought up. Certain persons have isohaemolysins in their blood which dissolve the red cells of other persons and in paroxysmal haemoglobinuria autohaemolysins may be present which can destroy the patient's own red cells. This autohaemolysis seems operative only when a low temperature is followed by a high one. When haemoglobinaemia exists the liver converts it into bile pigment causing bilious stools and jaundice. If one-sixth of the red cells are destroyed haemoglobinuria results.

Blackwater Fever.—The dark, porter-colored urine of blackwater is diagnostic even to the patient. The urinary sediment consists of granular debris with occasional haematoidin crystals. Albuminuria runs parallel with the haemoglobinuria. Pain in the loins, probably, from the plugging of the renal tubules by the detritus of red cell destruction, is a feature of blackwater fever. In blackwater fever we have the early appearance, even in a few hours, in a patient who is markedly asthenic and miserable, of jaundice, porter-colored urine and albuminuria.

Paroxysmal Haemoglobinuria.—Haemoglobinuria due to syphilitic infection. This condition is characterized by haemoglobinaemia, haemoglobinuria, fever, enlargement of spleen and positive Wassermann (90%). Chilling seems to be the essential factor for haemolysis in paroxysmal haemoglobinuria. The haemolyin is peculiar in that it will combine with the cells only at a low temperature. It has been suggested that there must be some constitutional individual peculiarity necessary to bring about the condition, as well as syphilis. Paroxysmal haemoglobinuria of the nocturnal type is discussed on pp. 149 and 1583.

Haemoptysis.—The spitting of blood is generally caused by disease of the lungs, bronchi, trachea or larynx. The determination of the source of the blood may at times be difficult. In haemoptysis the blood is generally frothy, mixed with sputum, alkaline in reaction and cough is present. The most common causes of haemoptysis are tuberculosis and mitral stenosis. However, paragonimiasis must be considered especially in endemic areas.

Hirudiniasis.—In Northern Africa, as well as in many islands of the Orient, the drinking water of ponds may contain leeches and these water-leeches tend to attach themselves to the pharyngeal mucosa. They may also attach themselves to the tissues about the larynx. In these cases we not only have cough and haemoptysis but dyspnoea from laryngeal oedema. It is probable that cases of dyspnoea called halzoun, and due to the attachment in the region of the larynx of flukes (*Fasciola hepatica*), as the result of eating raw liver, may sometimes be due to leeches, as the two affections occur in the same regions.

Paragonimiasis.—Infection with *Paragonimus ringeri* is popularly known as endemic haemoptysis for the reason that after violent exertion or at times without manifest reason, attacks of haemoptysis come on. The diagnosis is made by finding the operculated eggs in the sputum.

Haemorrhage.—The escape of blood from the vessels may be evident by epistaxis, haematuria, haemoptysis, haematemesis or other sources.

Ancylostomiasis.—There is a question to what extent the hookworms abstract blood from the intestines, although tests for occult blood are deemed important by some authorities in the diagnosis of this disease.

Beriberi.—Some consider ship beriberi may be of the nature of scurvy in which case one should have in mind spongy, bleeding gums and the intramuscular haemorrhages of scurvy.

Bilharziasis.—In vesical and rectal bilharziasis the perforation of the terminal branches of the portal vein by the terminal or lateral spined eggs frequently gives rise to haemorrhages.

Dengue.—In dengue we may have an epistaxis at the time of the crisis of the first febrile paroxysm.

Dysentery.—In dysentery the blood-admixed mucous stools are of diagnostic importance.

Infectious Jaundice.—Epistaxis is common. Intestinal haemorrhage and haematuria may occur. The diagnosis is made by the finding of spirochaetes by dark field in a blood or urine examination, or by guinea pig inoculation.

Leprosy.—In leprosy, epistaxis may be an early sign.

Malaria.—Epistaxis and alimentary tract haemorrhages are a common finding in the recognized haemorrhagic form of pernicious malaria.

Plague.—The damage to the endothelial lining of capillaries in plague gives rise to frequent haemorrhages into the skin.

Verruga.—The granulomatous lesions of verruga are haemorrhagic in character.

Yellow Fever.—During the asthenic period of the disease, which sets in about the fourth day, we have, as a result of the damage to the endothelial lining of the capillaries, various haemorrhages. Of these the best known and most dreaded is that from the stomach, black vomit. The bleeding from the gums is apt to appear before that from the stomach. Not only may bleeding occur from the intestines but from the mucosa, of the nose, conjunctiva or vagina.

Heart Involvement.—Under heart involvement have been included those tropical diseases which affect the cardiac muscle itself and those which cause a disturbance in the rate or rhythm which may be of importance in diagnosis, treatment or prognoss.

Ancylostomiasis.—Hookworm anaemia may cause early and marked cardiac ipalpitation. The pulse rate often averages about 110 and the blood pressure is low. There is often some right-side dilatation of the heart.

Beriberi.—Almost as important in diagnosis as the weakness of the legs, with anaesthetic and oedematous areas, is the early palpitation of the heart upon the slightest exertion. Later on as the vagal degeneration becomes more prominent there is a loss of the normal cardiac rhythm, to even become embryocardial, together with dilatation of the right heart, pulsating jugulars and various blowing murmurs, which are propagated into the vessels of the neck. The pulse is weak and rapid and this combination of a tumultuous heart action and weak pulse is striking. Blood pressure is below normal.

In acute pernicious beriberi, pulmonary congestion and oedema are often associated with the acute and severe heart manifestations. The diaphragm may become paralyzed in beriberi. Some authors refer to the dyspnoea of beriberi as the beriberic corset.

Cardiac involvement is also a feature of ship beriberi as well as of infantile beriberi. In the latter a marked hypertrophy of the right heart is characteristic.

Blackwater Fever.—A rapid, weak and low tension pulse is the common finding in blackwater fever.

Cholera.—In cholera the pulse is rapid and feeble during the stage of evacuation and with the onset of the algid stage we practically find a cessation of the circulation. The systolic pressure may fall as low as 65 or 70 mm.

Dysentery.—In bacillary dysentery the tendency to an increase in pulse rate may be of some value in differentiating it from amoebic dysentery.

Heat Stroke.—Cardiac tetany may simulate angina pectoris. The pain is excruciating and may produce sudden death.

Leprosy.—A rapid pulse, especially in the morning, is thought to be a feature of active leprosy.

Malaria.—Malaria generally gives a small, rapid, high tension pulse in the cold stage to become full and bounding in the hot stage. A cardiac type of pernicious malarial fever has been described, particularly by the French.

Plague.—In this disease there is a striking toxic action on the heart muscle so that there is often a soft, dicrotic pulse, rapid from the first and soon becoming thready. Patients with plague may die from cardiac failure upon getting up from bed.

Trypanosomiasis.—African trypanosomiasis shows a rapid pulse rate whether the patient has fever or not. In Brazilian trypanosomiasis the parasites may tend to invade the cells of the heart muscle thus producing manifestations of myocardial disease. The

parasite (*Schizotrypanum cruzi*) may also affect the adrenals, causing a low blood pressure along with other signs of Addison's disease.

Typhus fever is a disease which tends markedly to affect the heart. Along with faint heart sounds there is a rapid, low tension pulse.

Yellow Fever.—In yellow fever we have at first a high blood pressure. The pulse rate, which at first corresponds with the rise of temperature, soon shows Faget's sign—a falling pulse with a constant temperature or a constant pulse with a rising temperature. It is a markedly slow pulse after the third day. The blood pressure is low in the asthenic stage.

Heat, Effects of.—Smith, E. E., believes that heat stroke is a thermo-regulatory decompensation resulting from an imbalance of complex physical and physiological factors following exposure to heat. Vasomotor collapse may occur with resultant prostration without hyperpyrexia or the attack may be sthenic in type with hyperpyrexia and grave prognosis unless prompt therapy is instituted. Tetany may occur in either type and involves cardiac and plain muscle as well as voluntary muscle. Miners' and fireman's cramps are manifestations of tetany of voluntary muscle. Smith emphasizes the importance of tetany of the plain muscle of the intestine as a factor inhibiting water assimilation and the sudden death of sun stroke is attributed to cardiac tetany. The usual post mortem findings are generalized vascular congestion and petechial haemorrhages, accelerated decomposition, bacterial invasion, parenchymatous degeneration and rigidly contracted left ventricle, pylorus and colon. This spasticity does not persist long after death. Congestion, oedema and haemorrhagic effusion occur in the lungs and may be of extreme severity. Exposure to heat is the primary etiological factor causing thermo-regulatory failure. Contributory factors include insufficient water intake, associated incidental pathological processes and especially alcoholism. Dehydration, loss of chlorides and an uncompensated acidosis due to accelerated metabolism and decreased respiratory exchange result. Sudden death is attributed to tetany of the heart. Fatal cases that escape this hazard die from a variety of causes, the cause in any particular case depending upon a generalized physiological disorganization and inherent weakness in the particular individual.

Herpes Labialis.—Small clusters of vesicles on the lip commonly called fever blisters are a common finding in malaria (40%), pneumonia (40%), and cerebrospinal fever (30%).

Hookworm Disease.—See anaemia.

Hypertension.—Arterial hypertension increases with age. The more common causes of hypertension are nephritis, arteriosclerosis, syphilis, goiter, toxaemia of pregnancy and the menopause. Cerebral haemorrhage and tumor should be considered.

Hypotension.—A low systolic blood pressure is common in cholera, reaching a low limit of 60–70 mm. Hg. Tuberculosis and especially Addison's disease also give low readings.

Indicanuria.—In sprue and pellagra we have a rather marked increase in indican. It is probable that many cases of vague manifestations of neurasthenia with loss of physical and mental energy are connected with autointoxication rather than tropical heat or intestinal parasites.

Infectious Jaundice.—Sudden onset with chill, headache, intense injection of the eyes, vomiting and muscular pain. Jaundice occurs on 3rd or 4th day. Fever falls by lysis after 3 or 4 days. Following a few days of moderate fever a second rise occurs. Rapid pulse and clouded consciousness help differentiate yellow fever. The blood and urine should be examined microscopically for Leptospira and guinea pigs should be inoculated with the patient's blood.

Insomnia.—Sleeplessness or, at any rate, a condition where the patient only dozes is often seen in dengue. This mental alertness and wakefulness may also be noted in yellow fever. In malaria, possibly connected with quinine administration, we may have marked insomnia although cases have been reported of insomnia due to malaria which has been relieved by quinine. Just as cardiac decompensation from any cause will be attended by a distressing insomnia so is this also a feature of beriberi where cardiac involvement is marked. Liver abscess may be attended with insomnia. Malta

fever is often attended with a weariness from suffering with the various joint and nerve pains so that insomnia is often marked. Even in trypanosomiasis insomnia may be present at first. Insomnia is also one of the early neurasthenic manifestations of pellagra.

Intestinal Tract.—It is usual to consider constipation as a clinical feature of such diseases as plague, yellow fever, Malta fever, beriberi and tsutsugamushi, as well as typhus fever. Abdominal pains are most often connected with dysenteric conditions and it is customary to state that the greater the tormina, or intestinal griping, the nearer is the dysenteric process to the caecum. In cholera the cramping of the abdominal muscles may follow that of the calf muscles. In sprue we may have a doughy sensation on palpating the abdomen due to the fermenting contents of the intestine. In the algid type of pernicious malaria the abdominal griping may be severe. Tenesmus is the condition which along with tormina is encountered in some forms of dysentery. In rectal schistosomiasis the thickenings and blood extravasations, resulting from the eggs extruded by the fluke, may give rise to prolapse of the rectum. This may also occur in severe bacillary dysentery and in a disease of British Guiana and Venezuela, known as epidemic gangrenous rectitis, prolapse and gangrene of the rectum may occur. The symptoms are those of gangrenous dysentery.

Jaundice.—The retention of serum bilirubin, producing yellowish or greenish yellow discoloration of the skin, is one of the most striking symptoms in clinical medicine. A skin pigmentation not due to the accumulation of bilirubin is not jaundice and other causes must be sought for, such as Addison's disease, diabetic bronzing and carotinemia. This differentiation by the van den Bergh test should be one of the first diagnostic steps taken when considering jaundice or skin pigmentations. If it is found that the discoloration is due to retention of serum bilirubin one may by the same test ascertain the type of jaundice present. Jaundice, from a clinical standpoint may be classified as: (1) Obstructive. (2) Haemolytic. (3) Toxic and infective (McNee).

In obstructive jaundice the reaction is always immediate and direct, and in haemolytic jaundice the reaction is a delayed direct one with a positive indirect reaction above normal. The toxic and infective type of jaundice occupies an intermediate position but usually giving a direct reaction. The recovery of a large quantity of bile from duodenal siphonage is indicative of haemolytic jaundice.

In obstructive jaundice there is a definite renal threshold and if the serum bilirubin reaches a higher concentration than 2 mg. per 100 cc. of blood, bilirubin appears in the urine. The kidneys are impervious to the serum bilirubin of haemolytic jaundice and no matter how high the concentration, no bilirubin appears in the urine, but urobilin appears instead. This explains the acholic urobilin icterus of pre van den Bergh days. There may be a deficiency of vitamin K.

Haemolytic Jaundice.—Serum bilirubin due to excessive red blood cell destruction may occur in: (1) Malaria. (2) Blackwater fever. (3) Paroxysmal haemoglobinuric fever. (4) Acquired and hereditary haemolytic jaundice. (5) Poisoning by snake venom. (6) Icterus neonatorum. (7) Transfusion with incompatible blood. (8) Pernicious anaemia. (9) Relapsing fever.

Toxic and infective jaundice is the most common type and occurs in: (1) Toxic, following chloroform, arsenic and carbon tetrachloride poisoning. (2) As a complication of acute infectious diseases such as yellow fever, Weil's disease, syphilis, pneumonia, septicaemia and acute inflammation of the bile ducts.

Dickens (Naval Medical School) working with the bromsulphthalein test observed that in malignancy of the liver there was a relatively low dye retention, the average being 27.3% at the end of 30 minutes. This, he explains by the fact that malignancy may involve only a portion of the liver tissue and its intrahepatic duct system, leaving the remainder free to excrete the dye. He believes that this would explain the seemingly paradoxical direct—immediate van den Bergh in such cases. This author believes this finding is of great differential diagnostic value. The autopsy findings in the cases reported would seem to support this view. He also advises the siphonage of the duodenum following the intravenous administration of the dye. If dye is recovered

from the duodenum by this procedure the common duct is patent. He believes this of considerable differential diagnostic value in distinguishing intrahepatic obstruction from extra-hepatic obstruction of the bile passages.

Arsenic Poisoning.—Jaundice is a characteristic symptom of acute or so called delayed arsenical poisoning. The appearance of this symptom is a contraindication to the continuance of arsenical medication.

Bilious Remittent Fever.—The jaundice appears rather earlier than that of yellow fever but is rarely seen on the first day of the paroxysm as with blackwater fever. Of great diagnostic value is the early appearance of bile-colored urine as different from the haemoglobin-tinged urine of blackwater. The albuminous urine of yellow fever is not apt to show any bile coloring in the first three or four days of the disease.

Blackwater Fever.—In a typical case of this disease we have within a few hours a marked jaundice which tends to deepen. It is usually more or less marked according as the haemoglobinuria may be. It does not show the tendency to persist as does the jaundice of yellow fever.

The van den Bergh test is of value in differential diagnosis. In blackwater fever it is delayed (indirect) indicating haemolytic jaundice. In spirochaetal jaundice the van den Bergh gives an immediate reaction with marked increase in color by the indirect reaction probably indicating infective jaundice.

Carbon Tetrachloride Poisoning.—In poisoning following carbon tetrachloride, jaundice generally occurs on the second day following its administration. The jaundice may be a most striking symptom and again we may have toxicity without jaundice. Jamson, Minot and Robbins state that jaundice may or may not be apparent but in their experience the cause of the intoxication is best indicated by the van den Bergh test. Calcium chloride or ammonium chloride has a marked effect in controlling the symptoms.

Carotinaemia.—The presence of a carotinoid pigment in the blood gives a striking resemblance to jaundice, however, the sclerae are not tinted. The definite recognition is by the van den Bergh test as in carotinaemia the bilirubin in the blood is normal. The icterus index will however measure the degree of carotinaemia.

Cirrhosis.—In those liver cirrhoses associated with Katayama disease and kala-azar there is no typical jaundice.

Hepatitis.—In tropical hepatitis or congestion of the liver or, as it is often termed, tropical liver, there is rarely a distinct jaundice and if such occurs it is only temporary. Such terms as earthy, muddy, sallow, sub-icteric or pale lemon tint are more often applied than jaundice.

Liver abscess rarely gives rise to a definite jaundice unless the abscess be so situated as to cause pressure on the bile ducts.

Liver Fluke.—In clonorchiasis, or the liver fluke disease of man, jaundice is not a feature of the disease except in the very late stages.

Malaria.—The jaundice in this disease is haemolytic in origin and the serum bilirubin parallels the destruction of the red blood cells. There is an increase in the serum bilirubin following each chill and this is of differential diagnostic importance. See malaria for laboratory diagnosis.

Pernicious Anaemia.—The skin pigmentation so characteristic of this disease is accompanied by bilirubinaemia. The diagnosis of pernicious anaemia is hardly tenable without a direct-delayed and indirect quantitative van den Bergh above normal. See pernicious anaemia for diagnosis.

Relapsing Fever.—There is a clinical type of relapsing fever associated with jaundice and a high death rate which was first described by Griesinger from Egypt. This icteric type is not infrequent in Asia. This jaundice is late and the disease much resembles yellow fever. The enlarged painful spleen and the finding of spirochaetes in the peripheral circulation are essential to differentiation.

Sickle-cell Anaemia.—Jaundice and anaemia are marked. Ulcers on shin, infantile sexual development and the finding of crescent shaped red blood cells are diagnostic.

Spotted Fever of the Rocky Mountains.—In severe cases of spotted fever of the Rocky Mountains we may have a generalized jaundice. Rarely cases of typhus fever may show jaundice.

Weil's Disease.—Much interest was aroused in Weil's disease, or epidemic jaundice, on account of the frequency of the disease in soldiers in the Balkan campaign and the outbreaks of it in central and parts of northern Europe and England, and its occurrence in the United States. A spirochaete was shown by Inada and others to be the cause. However, some workers reported the isolation of paratyphoid B organisms from the blood of such cases. Frugoni obtained cultures of this organism from the duodenal fluid of 11 cases from 48 cases investigated. The accepted cause of true Weil's disease is *Leptospira icterohaemorrhagiae.* The jaundice begins about the third day of an irregular fever. Like yellow fever these cases show injection of the conjunctivae and albuminuria. The cases, however, usually show a leucocytosis and enlarged spleen.

Yellow Fever.—Very important is the fact that the jaundice of yellow fever does not appear until late, about the third or fourth day. When jaundice appears earlier, as by the second day, the prognosis is almost surely a fatal one. The icterus is more marked about the face, neck and upper parts of the trunk. The albuminuria precedes the jaundice. There are cases which succumb without having shown jaundice but immediately following death the yellowish discoloration has been noted. At autopsy the yellow fever cadaver is almost invariably deeply jaundiced.

Joint Involvement, Diagnostic Significance of.—In considering the diagnostic significance of joint manifestations of tropical diseases, it is essential that the practitioner in the tropics bear in mind the cosmopolitan arthropathies. It should be remembered that lesions of joints may accompany or follow almost all infectious diseases, and that it is often impossible to ascertain if the lesions be due to the actual presence of organisms within the joint or to the action of toxic substances elaborated elsewhere; so that infectious arthritis is broadly defined as arising from the presence within the body of a focus of infection. This definition is further expanded to include joint affections of intestinal origin, and also those in which neither the causal organism nor its focus of origin is discoverable, but which by analogy we unhesitatingly recognize as being due to an infective agent. It is to be noted that the lesions of arthritis may develop either in the intra-articular membranes or in the bony parts adjacent to a joint, and that they may remain confined to their primary site or eventually extend to involve other tissues See muscle involvement and pain in bones.

Infectious Arthritis

A. Of known etiology.

May be acute or chronic. Examples are gonorrhoea, typhoid, tuberculosis, bacillary dysentery, pneumonococcus infections, pyogenic cocci, filariasis, Malta fever, secondary to any recognized focus.

B. Of unknown etiology.

May be acute or chronic. Examples are acute articular rheumatism; rheumatoid arthritis, four types beginning with acute symptoms, one type having insidious onset; and possibly hypertrophic arthritis. These several forms may be due to unidentified foci, often situated in the alimentary tract, or may represent allergic phenomena secondary to bacterial or other form of sensitization.

Noninfectious Arthritis

A. Traumatic.

1. Acute, due to known traumatism.
2. Chronic, generally static in origin, or due to chronic strain or irritation. Possibly includes villous arthritis of the knee and hypertrophic arthritis in the young.

B. Trophic.

1. Metabolic. Examples are gout, psoriasis and possibly hypertrophic arthritis
2. Senile.
3. Neuropathic. Examples are tabes, leprosy, syringomyelia and scleroderma.
4. Arteriosclerotic.

C. Blood dyscrasias, as haemophilia, anaemias and scurvy.

D. Toxic, as lead poisoning.

The diseases of more peculiar importance for the tropics in which joint involvement must be considered in the diagnosis are the following:

Bacillary Dysentery.—As far back as the 17th century (Sydenham) it was noted that joint pains or actual arthritides were occasional complications of dysentery. We now know that the bacterial types of dysentery are those most likely to show joint complications. Because the joint fluid in these lesions is usually sterile, it is assumed that they are the effect of toxins (or a toxin) produced by the dysentery bacillus. Of the two hypothetical toxins of the dysentery bacillus one is supposed to produce neuritis and joint complications. Arthritides are more common in some epidemics than in others and with certain strains of bacilli than with others. The Shiga strain is the worst offender in this regard. Manson reported 27% of joint involvement in one epidemic.

Clinically, dysenteric arthritis is more apt to affect one of the larger joints, the knee, ankle and hip, being most affected. The elbow, wrist or shoulder joint may be affected, though this is unusual. The pain and swelling may be an incident of the early part of the attack. Usually it comes on when the acute symptoms are abating or as a sequel. The joint is distended with effusion and this involves the ligaments around the joint. Given an arthritis in the course of a frank dysentery there is nothing it could ordinarily be confused with. It is well to remember, however, that patients with dysentery may have also a concurrent gonorrhoea or arthritis from some focal infection. The dysenteric rheumatism ordinarily completely subsides with the cure of the colitis. In hepatic abscess following amoebic colitis pain of some type is a frequent symptom. Rheumatic-like pains and swelling of the hands occur rarely, rapidly disappearing when the abscess is evacuated.

Dengue.—Sporadic dengue is difficult to diagnose. In an epidemic the characteristic pain referable to tendinous insertions about joints are present in at least 50% of cases and is of great diagnostic value. There is no swelling of the joints although the turgescence of the skin over them may give the impression of an arthritis. The intensity of pain varies from a feeling of muscular soreness to excruciating pain when muscles or joints are actively moved. Passive movement is not usually painful. In addition to the rachialgia, bone and joint pains, some writers have described swelling of the joints. This last in Stitt's experience is unusual. Joint pains are so characteristic that they distinguish dengue from all other eruptive fevers.

Joint pains during convalescence may produce stiffness and crippling continuing for many weeks after the cessation of fever.

Filariasis.—Maitland and Manson-Bahr have noted a synovitis which is apparently a complication of filariasis. The latter has found a fibrotic ankylosis often to follow such a joint condition. The synovitis may be followed by pus formation with serious or fatal outcome.

Guinea Worm Disease.—Rarely the female *Dracunculus* may penetrate a joint and cause synovitis or arthritis.

Leprosy.—Occasionally there is joint involvement, especially of the wrist and ankle joints, in which erosion of the cartilage and bone dislocation occur giving us a condition similar to the Charcot joint. It will be remembered that the Charcot joint is most often seen in tabes and may give one of the greatest joint swellings. As a rule only one joint, usually knee or hip, is involved in tabes and the affection is generally painless. The progress may be acute, subacute or chronic. Syringomyelia, a disease which may be confused with leprosy, may also show joint involvement, usually of the upper extremity.

Relapsing Fever.—Bone, muscle and joint pains are practically always present in this disease. In addition rachialgia and headache are prominent symptoms and the aching gnawing pains in loins or nape of neck may make one think of beginning smallpox, dengue or yellow fever. There is no swelling of the joints in relapsing fever. As in dengue the pains in the neighborhood of the joints may be quite persistent.

Undulant Fever.—This infection offers a good example of a disease in which joint symptomatology is of diagnostic and therapeutic importance. A prolonged typhoid-

like course with sudden and painful swelling of various joints, hip, shoulder, ankle or costo-vertebral articulations, if occurring in an endemic area of Malta fever, would at once make one suspect this disease. Typhoid does not give painful joints, dengue is not accompanied by joint swelling, while gonorrhoeal polyarthritis will be accompanied by other evidence of gonorrhoeal infection. The neuralgias, sciaticas and painful joints, together with the sweats which exhaust the sufferer from Malta fever, often tempt both patient and physician to resort to narcotics. Rogers found acute or subacute effusion into one or more joints was present in at least 40% of cases of Malta fever. The Malta fever joint is not red, which fact, taken with its evanescent character, differentiates it from the arthritis of acute rheumatic fever.

Yaws.—This disease may cause bone, joint and muscle lesions similar to those of syphilis. From the mother lesion to the tertiary framboesioma the course and symptoms of the two diseases may be similar. Thus we may have the flying pains and osteocopic pains of the early days of infection and, as later events, chronic synovitis, framboesial infiltration of perisynovial membranes, framboesial infiltration of synovial membranes, chondro-arthritis, epiphysitis and chronic framboesial periostitis. These pathological processes cause such conditions as we know under the names dactylitis, saber shin, mutilating oro-rhino-palato-pharyngeal ulcerations, Parrot's nodes and craniotabes. The uncomplicated framboesioma may sometimes resemble the gumma. Certainly the later effects of bone and joint destruction and scarring are wonderfully like some of the middle-age European descriptions "when lues was in flower." In framboesial disease the damage from bone destruction or from contracture following cicatrization may be so complete as to render useless a finger, a hand, one of the large joints or even a whole extremity.

Kala-azar.—See leishmaniasis.

Kerandel's Sign.—Deep hyperaesthesia accompanied by pain, often retarded, after some slight blow upon a bony projection of the body is characteristic of trypanosomiasis.

Lachrymal Obstruction.—Elliott notes the extreme frequency of this condition in India, and states that in the Madras Ophthalmic Hospital 125 operations for excision of one or both lachrymal sacs were performed.

Leishmaniasis.—Under this heading four diseases may be grouped; visceral leishmaniasis of adults or kala-azar, infantile kala-azar, cutaneous leishmaniasis or Oriental sore and American leishmaniasis. Diagnosis of visceral leishmaniasis: (1) Double rise of temperature in twenty-four hour period. (2) Splenic enlargement. (3) Marked leucopenia. (4) Anaemia. (5) Demonstration of *Leishmania* by blood examination or splenic puncture. See p. 273.

Oriental Sore.—This condition must be differentiated from syphilis. The finding of *Leishmania* is diagnostic. Oriental sore is often accompanied by fever. The ulcer is painless.

Leprosy.—Leprosy is divided into two well separated clinical types. (1) Nodular or skin leprosy which is characterized by granulomatous proliferation of corium and lymphatic glands. This form shows nodular infiltration, chiefly about the ears, nose, eyebrows and the extensor surface of the forearms. (2) Nerve or maculo-anaesthetic leprosy which is characterized by nerve thickening, flat anaesthetic spots, chiefly on covered regions of body and muscular palsies and atrophies. When the two types are associated we have mixed leprosy.

Leucocytosis.—It is to an increase in the polymorphonuclears that this term is usually applied, the term lymphocytosis or eosinophilia being employed where white cells of lymphocyte or eosinophile nature are increased. We have physiological leucocytosis in the later weeks of pregnancy, also in the new-born, and in connection with digestion. Toxaemic conditions as uraemia, diabetic coma and poisoning by CO tend to show a leucocytosis.

Brain Abscess.—The leucocytes rarely exceed 15,000 in brain abscess.

Endocarditis.—A marked leucocytosis is of diagnostic importance in acute ulcerative endocarditis provided it is not fulminant in type. In subacute endocarditis there is usually only a moderate increase in the number of leucocytes.

Erysipelas.—This condition is generally accompanied by a leucocytosis of from 15,000 to 20,000.

Liver Abscess.—Rogers reported that in liver abscess, with a leucocytosis of 15,000 to 20,000 we have only about 75 to 77% of polymorphonuclears—there being also a moderate increase in the percentage of large mononuclears.

Malignancy.—The blood of cases with malignant tumors tends to show a moderate leucocytosis except in epithelioma of the skin. When a cancer is ulcerating quite a high white count may be obtained.

Meningitis.—With meningitis counts of 25,000 are not unusual. Epidemic cerebrospinal meningitis also gives a leucocytosis of from 15,000 to 20,000.

Plague.—We usually have a marked leucocytosis due to a great increase in the polymorphonuclears. The white count may exceed 50,000. Just as septicaemic plague may so overwhelm the organism that it does not respond with fever so may the leucocytosis be absent. Bubonic and pneumonic plague tend to become septicaemic, so that in such types of the disease we may often obtain a definite diagnosis from blood cultures, while in bubonic plague a microscopical preparation or culture from the bubo is usually diagnostic.

Pneumonia, Lobar.—In this disease we have a leucocytosis of 20,000 to 30,000 or higher. The eosinophiles are almost absent. A normal leucocyte count makes the prognosis unfavorable.

The leucocyte count drops about the time of the crisis, and with the reappearance of eosinophiles is a favorable sign.

Relapsing Fever.—Spirochaete fevers, as relapsing fever, may give a leucocytosis of from 25,000 to 50,000 when accompanied by high fever and bronchitis. The average count gives a leucocytosis of from 12 to 15 thousand with a polymorphonuclear increase to between 75 and 80%. The normal percentage of large mononuclears helps in the differentiation of malaria. The leucocyte count tends to be higher about the time of crisis. The diseases most likely to be confused with relapsing fever are malaria, dengue and yellow fever. The finding of the malarial parasites or spirochaetes will differentiate these diseases. The leucocyte count is higher in relapsing fever, and in malaria the afebrile period is shorter. There is a leucopenia in dengue. There is no leucocytosis in yellow fever while malaria and especially dengue generally show a leucopenia.

Septic Processes.—The leucocyte count is of great value, especially when we obtain a leucocytosis with 80 to 90% of polymorphonuclears, as in appendicitis, cholecystitis, or other suppurative conditions.

Smallpox.—Smallpox, especially at time of pustulation, usually gives a leucocytosis of from 12,000 to 15,000. Smallpox often shows a very large percentage of very characteristic large mononuclears.

Leucopenia.—This is a term used to designate a reduction in the normal number of leucocytes. A leucocyte count of 5000 would represent a slight leucopenia; one of 2000, a marked leucopenia. In the later stages of typhoid, and in acute miliary tuberculosis, we expect a moderate leucopenia. Glandular tuberculosis may give a very marked leucopenia. Tuberculous peritonitis will show moderate leucopenia or a normal count. Agranulocytic angina also gives rise to marked leucopenia primarily of the granulocytes.

Dengue.—In this disease a leucopenia, which begins to show itself by the second day, is very characteristic. The average leucocyte count is about 3500 and along with this we have a reduction in the percentage of polymorphonuclears to about 50%. Towards the end of the terminal fever we have an increase in the percentage of large mononuclears.

Exophthalmic Goiter.—Kocher notes that in exophthalmic goiter the leucocyte count is considerably diminished and that the polymorphonuclears are not much more than one-half the usual percentage while the percentage of the lymphocytes is almost double the normal.

Influenza.—Influenza shows a leucopenia. The very fatal pneumonias of the 1918 epidemic of influenza showed a marked leucopenia.

Kala-azar.—In this disease there is a marked leucopenia. Kala-azar must be particularly differentiated from Banti's disease, malaria and undulant fever.

Malaria.—During the apyrexial period of malaria we may have a white count of 5000.

dementia praecox, general paresis, various manifestations of cerebral syphilis and acute maniacal or confusional states. Not only were all forms of mental disorder known in European countries represented, but their comparative frequency and the types of conduct exhibited were, on the whole, what might be expected in the study of a group of similar cases encountered in any other part of the world.

Overbeck-Wright in his book—"Lunacy in India"—notes that 44% of cases were under treatment for various types of mania, 15.9% for melancholia, 4.8% for delusional insanity, 5.2% for idiocy, 5.7% for dementia and 6.6% for insanity following the use of *Cannabis indica*. It is noted that dementia praecox is not included in the statistical returns, but the author states that in his experience hebephrenia and katatonia account for a much larger proportion of cases than melancholia.

Overbeck-Wright is of the opinion that general paresis is quite common in India notwithstanding the fact that for many years the opinion has obtained that syphilis of the central nervous system and the parasyphilitic diseases were exceedingly rare among tropical natives. He regards the incidence of cerebral disease in syphilitic natives as less than with Europeans, attributing this fact to the existence of an immunity acquired through the prevalence of syphilis among these people during a period of several centuries. Cases of general paresis are generally reported under the diagnosis of chronic mania.

Van Loon, from studies made in Java, concludes that a mistake is made in most books on tropical medicine as to the rarity of general paresis. Palthe (1936) has found in Java that the amount of dementia paralytica in the hospital wards was about the same for Europeans as for natives, but it was seen twice as frequently in Chinese as among the natives. Obviously the European population is much smaller than the native. Palthe emphasizes that one should not generalize that his statistics are applicable to other tropical countries. Stitt has pointed out that general paresis being a disease in which we have such characteristic laboratory diagnostic tests, especially the colloidal gold test, there should be little difficulty in settling this question of its absence or relative infrequency among natives of tropical regions.

Lymphocytosis.—Young children have normally an excessive proportion of lymphocytes even to a reversal of the polymorphonuclear-lymphocyte relation of adults. This is apt to be particularly marked in hereditary syphilis. Enlarged tonsils may give rise to lymphocytosis of 10,000 to 15,000 when more than 50% of the white cells may be lymphocytes. Rickets and scurvy also cause a lymphocytosis. Of course, the disease in which there is the most marked lymphocytosis is lymphatic leukaemia.

Glandular fever (Pfeiffer, 1889) (*infectious mononucleosis*) is a mild acute febrile disease, the fever coming on after a short incubation period and lasting from one to several weeks. Throat infections, particularly Vincent's spirillosis, have been thought by some to be concerned in its genesis. Clinically, it is characterized usually by sore throat, swelling of the cervical glands, and general glandular enlargement of variable degree and often enlargement of the spleen. Recovery practically always occurs within a few weeks. The total leucocyte count is usually from 10,000 to 12,000, with a lymphocytosis of from 50–90%. In some cases there is a normal total count, or there may be a leucopenia. The lymphocytosis may not reach its peak until after one or two weeks. The characteristic feature of the blood is the larger number of pathological lymphocytes present. Paul and Bunnell (1932) found that the serum in most cases after 7–10 days showed an increase in agglutinins of sheep red blood cells. Bailey and Raffel (1935) have found that this is unlike heterophile agglutinins, being absorbed by autoclaved ox cells but not by suspension of guinea pig kidney. A positive reaction is indicated by the disappearance of agglutinin in the serum extracted with autoclaved ox cells and by its persistence in that extracted with guinea pig kidney.

Undulant Fever.—Malta fever is a disease which may show quite a lymphocyte increase, this in association with a reduction in the polymorphonuclears.

Whooping-cough may cause a lymphocytosis of 20,000 to 30,000.

Malaria.—Characteristics of this disease are: (1) Presence of malarial parasites in blood. (2) Periodicity of chill and fever. (3) Splenic enlargement (4) Response to quinine. (5) Presence of melaniferous leucocytes. (6) Increase in mononuclear leucocytes when a leucopenia is present.

man may sometimes serve as the intermediate host through the accidental self-infection with the eggs of *T. solium.* Such infection may result either from contaminated hands or by ripe proglottids being carried back to the stomach by reverse peristalsis. The embryos then may migrate to almost any organ, especially the muscles, and in many, instances the brain with symptoms of epilepsy. The common tape worm of man, *Taenia saginata*, is found in the human host only as a sexually mature parasite in the intestines; there is never a cysticercus stage in the muscles.

Mycoses.—The best known mycoses of the tropics are the following: (1) Mycetoma a disease caused by various fungi invading, most commonly, the foot, which is honeycombed by numerous granulomatous areas from which lead sinuses, which discharge yellow or black granules, and eventually lead to disorganization of bone and other tissues of the foot. (2) Tinea imbricata, a ringworm-like affection of the skin, which gives rise to papery scales, arranged in rosette shapes, and without inflammatory characteristics. (3) Tinea cruris, the well known "dhobie itch" of the Orient, in which ringworm-like affection of the crotch, the itching is excessive. (4) Piedra, which is due to a fungus affecting the hairs, especially of the head, and having gritty nodules along the course of the hair. (5) Pinta is a variously coloured skin affection was formerly thought to be due to various fungi. For other mycotic infections and their diagnosis see pp. 1147–1197.

Myiases.—These are diseases caused by the invasion of various fly larvae, and may be divided especially into cutaneous myiasis, intestinal myiasis and nasal myiasis.

Cutaneous Myiasis.—In tropical America boil-like lesions may occur from the development of the larva of a species of botfly, in any skin area unprotected by clothing. In Africa there is a similar type of lesion, caused by the larvae of another fly. (*Dermatobia* and *Cordylobia.*)

Intestinal Myiasis.—Vague intestinal disturbances or violent abdominal pains may be caused by the presence of the larvae of various fly species in the intestinal tract. The infestation may be accompanied by fever and other symptoms. It is probable that the eggs of the flies gain access to the alimentary tract by being deposited on the food.

Nasal Myiasis.—In the tropical and subtropical parts of North and South America a fly, *Chrysomyia macellaria* is apt to deposit its eggs about the nasal orifices of persons with an offensive discharge from the nose. The fly seems to be attracted by foul odors. The larvae which develop are called "screw worms" on account of the segmental bands of bristles and tend to invade the various sinuses, causing great destruction of tissue.

The case sets in with signs of a very severe coryza, together with fever and marked frontal headache. The face becomes swollen, red, and tender in the region of the nose. As the larvae reach maturity they come out of the nose. A nasal douche of 15 parts chloroform in 100 parts milk is often efficacious in bringing away the larvae. At times *Sacrophaga* larvae may be found. See p. 1512 for other forms of myiasis.

Nausea and Vomiting.—So many diseases are attended with nausea, besides those in which nausea is accompanied by rather constant vomiting, that it would hardly seem advisable to consider it alone. At the same time the slight nausea which often accompanies bacillary dysentery, as one of the manifestations of toxaemia, may suggest this type of dysentery rather than the amoebic one.

Beriberi.—Vomiting is often a sign of dangerous vagal involvement in acute pernicious beriberi. Some consider that the extreme dilatation of the right heart, pressing on the stomach, may be the excitant of this vomiting.

Bilious Remittent Fever.—Bilious vomiting is the feature in bilious remittent fever which causes the patient the greatest distress.

Blackwater Fever.—In blackwater fever the frequent retching and bilious vomiting tend to exhaust the patient and the persistent vomiting of green bile often precedes death.

Cholera.—The vomiting of cholera follows the diarrhoea. The material vomited may be of the same character as the rice-water stools.

Liver Abscess.—Rarely a liver abscess may burst into the stomach, in which case there is usually vomiting of pus. Of course the more common route of rupture is by

the lungs in which case the chocolate-colored liver abscess pus would be coughed up instead of vomited up.

Relapsing Fever.—Bilious vomiting may be a striking feature of the icteric type of relapsing fever.

Vomiting Sickness.—There is a disease known as vomiting sickness which has been noted in Jamaica. It occurs chiefly in children and has a sudden onset with marked vomiting followed by cerebral symptoms and great mortality. Some thought the disease to be yellow fever but the fever and jaundice of that disease are absent. It is now recognized as due to ackee poisoning. See p. 1205.

Yellow Fever.—In yellow fever there may be early vomiting of whitish or bile-stained mucus but the well-known black vomit is a later feature, only occurring after the fourth day when the other haemorrhagic manifestations set in.

Neuritis.—Inflammation of a nerve, accompanied by pain and tenderness over the nerves involved, with disturbance of sensation, paralysis, and disappearance of reflexes may be: (1) Traumatic. (2) Chemical. (3) Infective. (4) Metabolic in origin. The first step to an understanding of neuritis is to determine the probable cause. Blumer states, "Bearing in mind the seat of the lesion in multiple neuritis from different causes, may prove helpful in the diagnosis. Generally speaking the following distribution is observed: Alcoholic, chiefly feet; lead, chiefly wrists; arsenic, all four extremities; beriberi, all four extremities; pellagra, all four extremities; diphtheria, palate, rarely all four extremities; puerperal, ulna and median, sometimes all four extremities."

Alcohol.—History of alcoholism; a bilateral neuritis. Pain and tenderness in the soles of the feet; foot drop; may have wrist drop; tender muscles; loss of deep reflexes; tactile anaesthesia with hyperalgesia in the feet is characteristic. Korsakoff's syndrome; the loss of memory for recent events, in a person who delights in fabrication of stories and reminiscences, which he himself believes, followed by hallucinations, illusions, delusions, and disorientation as to time, place and person, completes the picture of Korsakoff's psychosis.

Arsenic.—Arsenical neuritis may follow acute or chronic arsenical poisoning—all four extremities are involved as a rule; gastro-intestinal disturbances, enlargement of the liver, jaundice and skin pigmentation help differentiate from other conditions. Haemorrhagic encephalitis is a common occurrence from the so called delayed arsenical poisoning. The van den Bergh test is of aid in diagnosis.

Beriberi.—Beriberi produces a polyneuritis. Helpful points of diagnosis are: (1) History of dietary deficiency. (2) Oedema (wet beriberi). No other form of neuritis is accompanied by oedema. (3) Loss of deep reflexes. (4) Ankle drop. (5) Anaesthesia and numbness of skin. (6) Jongkok test—the patient is unable to rise from a squatting position if hands are placed over his head. In dry beriberi the dietary history and the onset of muscle tenderness, pain and weakness with dyspnoea and palpitation, accompanied by dilated right heart and attacks of angina are suggestive of beriberi. The neuritis of beriberi simulates and must be distinguished from neuritis produced by arsenic, lead, alcohol and pellagra.

Botulism.—The gastro-intestinal disturbance following dizziness and diplopia should make one think of botulism. This condition resembles encephalitis lethargica, anterior poliomyelitis, Landry's paralysis, and the paralytic form of rabies. The finding of the *Clostridium botulinum* is most important in diagnosis. For the demonstration of the toxine in the ingested food, filtered extracts of it should be injected into normal guinea pigs and in guinea pigs with immune serum.

Diabetes.—A polyneuritis characterized by pain, paralysis and atrophy of the lower extremities is characteristic of diabetes. The finding of glycosuria and hyperglycemia is diagnostic.

Diphtheritic Paralysis.—History of sore throat, involvement of palate without oedema and failure of pupil to react to accommodation or light should help in the diagnosis.

Leprosy.—The spots in nodular leprosy show loss of pain and temperature sense with retention of touch sensation.

Pellagra.—The history of defective diet, symmetrical erythema, more intense on those parts of the body which are not covered by clothing, tremor of tongue, weakness of

legs, pain on pressure in the dorsal region of the back and confused mental state suggest the diagnosis of pellagra.

Syphilis.—In syphilis there is slow onset, widely distributed neuritic pains and history of initial lesion. Positive Kahn blood serum reaction is usually present.

Undulant Fever.—Very characteristic are the sudden and painful joint swellings accompanied by various neuralgias, such as sacro-iliac pain and sciatica.

Diseases with Symptoms Which May Be Confused with Neuritis

Trichinosis may be confused with neuritis. This condition gives rise to pain and tenderness in the muscles which do not follow the nerve distribution. Eosinophilia, history of eating raw meat, oedema of the lids and muscle pain should help to differentiate. The finding of *T. spiralis* in portions of excised muscle is diagnostic. In rat bite fever there is pain in the legs without paralysis or disturbance of reflexes or neuritis. Dengue, Malta fever and yellow fever produce acute general pain in the limbs but not neuritis.

Nodules.—Small raised nodules appearing on the ear, eyebrow, cheek or chin should make one suspicious of leprosy. Leishmania nodules are small pinkish elevations seen in the non-ulcerative keloid type of oriental sore. Cutaneous nodules or tumors are the most striking clinical feature of onchocerciasis. Juxta-articular nodules are sometimes found in association with onchocerciasis and also in yaws. Differential diagnosis may be made by puncture and demonstration of microfilariae.

Oedema.—Oedema may be circumscribed or local or may be general. The chief causes of general oedema are—heart failure, renal insufficiency, angioneurosis, ancylostomiasis, idiosyncrasy to certain drugs such as potassium iodide and aspirin and snake bite. It is usually not difficult to ascertain the cause of a generalized oedema. The oedema due to heart failure affects particularly the dependent parts of the body. If the patient is up and about it is found that the lower extremities become oedematous, while if the patient is in bed the lower spine area becomes oedematous. The oedema of nephritis is generalized and shows no predilection for the dependent parts.

Abscesses, cellulitis and external or superficial tumors produce local oedema. In erysipelas there is swelling and tension of the skin with an advancing ridge raised and well defined. There is usually oedema and bulging over the mastoid in acute infections of this region. Empyema not infrequently is accompanied by oedema and passive congestion. Aneurysm of the arch of the aorta may produce oedema of one arm or of one side of the face as result of presure on the adjacent vein. In angioneurotic oedema there may be local oedematous swelling of sudden and transient duration. Tumors involving the mediastinum may show unilateral or bilateral oedema together with tortuosity of the superficial veins of the face, neck, arm or chest wall. Perinephric abscess may show oedema or puffiness over the loin. Trichinosis is frequently accompanied by oedema particularly of the face and about the eyes. Other less common causes are urticaria, erythromelalgia, sinus thrombosis, intermittent hydrarthrosis, tabes dorsalis and purpura haemorrhagica. Oedema, especially about the ankles, is to be looked for in all the secondary anaemias of the tropics, particularly malaria and ancylostomiasis.

Beriberi.—The oedema begins at first about the feet, especially about the dorsal junction of phalanges and metatarsus. It is characteristically pretibial. It may remain confined to the shin or go up to the knees, scrotum, sternal region or trunk. It is generally symmetrical but may be unilateral. It may become a general anasarca, even in forty-eight hours. The swelling of the face is at times enormous, the eyelids being so oedematous that the patient can see only by separating them with the fingers. The oedema is more solid than that of nephritis. It not only rapidly appears but disappears as rapidly. The oedema of beriberi may involve the glottis (oedema of glottis). Oedema of genital regions is less marked than in nephritis or cardiac disease. We may also have localized areas of oedema 3 or 4 inches in diameter. Ship beriberi, which has points in common with both beriberi and scurvy, reveals oedema which may be limited to the lower extremities or generalized. Epidemic dropsy is a type of beriberi in which there is fever and an erythema over the dropsical areas.

Calabar Swellings.—These seem connected with infections with *Loa loa.* The swellings originate suddenly and disappear in three or four days. They are hard and do not pit on pressure. These smooth swellings, often 2 to 4 inches in extent, are most often seen on arms, face or ankles. It is suggested that they represent an allergic reaction on the part of the tissues in response to the filarial toxine.

Katayama Disease.—The urticarial areas of oedema have given it the name of urticarial fever. See p. 1425.

Trypanosomiasis.—The oedema of the face and especially the eyelids may be striking especially in children in Chagas's disease. There may also be patches of oedema elsewhere.

A peculiar disease of North China, known as atriplicism, is caused by the eating by the very poor of a weed, *Atriplex*, common around Pekin. There is itching of the fingers, quickly followed by swelling. This tends to extend to the back of the hands and up the outer surface of the forearm. The face becomes so swollen that the eyelids may be closed. See p. 1201.

Pain.—Cephalalgia, rachialgia and the characteristic pain of certain diseases give considerable information in establishing a diagnosis.

Beriberi.—In beriberi there is often pain in the epigastric region so that the slightest touch causes great distress. This epigastric tenderness is also a feature of yellow fever. The calf muscles are also markedly hyperaesthetic in beriberi.

Blackwater Fever.—Pains in the lumbar region giving expression to the kidney damage done by the haemoglobin detritus plugging the tubules, is a common symptom in blackwater fever.

Cholera.—In cholera one of the most striking phenomena of the disease is the terrible cramping of the muscles, especially those of the calves and feet. These pains actually torture the patient.

Dengue gives rise to a marked post-orbital soreness rather than pain. There is also a marked rachialgia with pains in the limbs often referred to the regions of the joints, which, however, are not swollen.

Heat Stroke.—Cramps of abdominal muscles as well as those of extremities are often noted in heat stroke in men in firerooms.

Leprosy.—In leprosy the neuralgic pains may be very severe through the inflammatory reaction while the nerves are being pressed upon by the connective tissue increase of the endo- and perineurium. Mention has been made of excruciating pains of the toes, especially the big toe, even suggesting gout.

Malaria.—In all forms of malaria, but especially in the paroxysms of malignant malaria, there are severe headaches and pains in the extremities. Intermittent neuralgia is often regarded as malarial.

Oroya Fever.—In this very serious disease of certain areas of Peru the bone pains may be severe. These bone pains have been reported as especially marked in the sternum but also as involving the long bones.

Pellagra.—Pain on pressure on dorsal or lumbar spine is common in pellagra.

Plague may be associated, during the first day or two, with an excruciating headache. This may even be prodromal but tends to disappear with the rapidly developing stuporous state of the patient.

Relapsing Fever.—Bone pains, especially referred to the knees, are complained of by patients with the bilious typhoid of Griesinger. This is a type of relapsing fever occurring in Egypt.

Trench Fever.—Pain over the shin bone is a prominent complaint in this affection so that the term "trench shin" has been employed.

Trypanosomiasis.—In trypanosomiasis headache is often marked, together with a characteristic deep hyperaesthesia, so that the striking of a limb against a hard object gives rise to excruciating pain, there being, however, a delay in the experiencing of the painful sensation (Kérandel's sign).

Undulant Fever.—In Malta fever the neuralgias, especially sciatica, often associated with suddenly appearing, painful joint swellings, are prominent features.

Yellow fever is marked by pains in the lumbar region, the *coupe de barre* of the French, as if the patient had been beaten over the small of the back with a bar of iron. The

headache is rather orbital and is often excruciating. There are also frequently heavy, dull pains of the extremities.

Oroya Fever.—See anaemia and verruga.

Paragonomiasis.—See haemoptysis.

Paroxysmal Haemoglobinuria.—In this condition we have haemoglobinuria, haemoglobinaemia, fever, enlargement of the spleen and liver, and occasionally jaundice, while in blackwater fever jaundice comes on early and is marked. The cause of paroxysmal haemoglobinuria is not definitely known but in the type incited by cold there seems to be as definite a relationship to syphilis as blackwater fever has to malaria. Reports show 90% have a positive Wassermann and recovery under antisyphilitic treatment has frequently been reported. The Donath Landsteiner reaction is positive. This disease is characterized by paroxysms of haemolysis within the blood vessels. All the signs and symptoms of this condition may be attributed to the rapid haemolysis of a large number of red blood cells. In malaria, jaundice is more marked than in paroxysmal haemoglobinuria. For nocturnal paroxysmal haemoglobinuria in which the Donath Landsteiner test is negative see Blackwater fever, pp. 148 and 1583.

Pellagra.—In a typical case there is the diagnostic pellagrous symptom-complex: (1) Symmetrical sharply outlined erythema. (2) Alimentary tract disturbances, stomatitis, epigastric burning and diarrhoea. (3) Neurological manifestations. (See neuritis.)

Periodicity.—*Malaria* shows a typical periodicity of paroxysms of chill, and elevation of temperature. Malarial paroxysms show a preference for the forenoon or early afternoon. In malignant tertian there is a prolonged hot stage, with gradual onset and the fever tends to remit or may remain continuous for several days. The study of such a chart is apt to show slight rises every other day.

Pyelitis.—This condition at times gives a regular periodicity of chills and fever resembling malaria. Ultimately the fever assumes the "picket fence" type. Unilateral pain, tenderness in the loin with frequency of urination are common. Urinary findings and negative blood film for plasmodia differentiate from malaria.

Relapsing Fever.—Three or more pyrexial periods weeks apart are typical of relapsing fever.

Trench fever frequently shows pyrexial periods, recurring after 5–7 days. The number of relapses of fever varies greatly; from 3 to 5 are common.

Undulant Fever.—Wave-like periodicity of fever lasting for seven to ten days and separated by afebrile intervals may suggest the diagnosis. However, this periodicity is frequently absent.

Phlebotomus Fever.—(1) Presence of *Phlebotomus papatasii.* (2) Sudden onset, temperature 103–104°F.; frontal headache, usually post-orbital; eyeballs tender to pressure. (3) Marked injection of conjunctivae, the injection usually extending in a horizontal band across the eyeball. (4) The face and neck are flushed, the redness resembling a rash which according to Castellani persists for 10 to 15 days after the fever subsides and fades away very slowly. (5) Presence of sand-fly bites as red punctures, usually about the wrist and ankles. (6) Leucopenia. The fly penetrates 18 mesh screen.

Photophobia.—Influenza, measles, quinine poisoning, trichinosis, typhus fever, small pox, sun light and syphilitic pachymeningitis are common causes of photophobia encountered in the tropics. Ocular onchocerciasis also gives rise to photophobia in Guatemala, Mexico, and parts of Africa.

Plague.—Clinically plague is divided into a mild form known as pestis minor and a severe form pestis major.

Pestis Minor.—(1) Ambulatory form. (2) Slight fever. (3) Little prostration. (4) Primary vesicle or phlyctenule at site of the flea bite.

Pestis Major.—In the more common and more serious forms of plague we have two distinct types (*a*) bubonic plague and (*b*) pneumonic plague. Septicaemia is common in both forms and is often recognized as a separate type—septicaemic plague.

Common to both forms are sudden onset, rigors, rapidly rising and irregular temperature, great prostration, confused mentality and inco-ordination of speech, with rapid, weak pulse.

Bubonic.—The pathognomonic painful bubo appears about the third or fourth day. The buboes appear in the inguinal region involving the femoral glands (70%), axillary (20%) and the submaxillary and cervical (5 to 10%). Very characteristic of plague buboes is the oedema of the periglandular tissue.

Pneumonic.—In the course of an attack of pestis major without buboes we may have grave pulmonary symptoms develop. Early dyspnoea, shallow respiration with the expectoration of abundant watery sputum, which later becomes blood-tinged and absolutely sanguineous without seemingly sufficient chest findings, should make one gravely suspicious of plague. There is never the rusty tenacious sputum, herpes or painful respiration of lobar pneumonia.

Polycythemia.—An increase in the red blood cells is noted in cholera to 8 to 9 millions. A high red cell often occurs in Sorroche (Peruvian mountain sickness) and in the natives who reside in the high altitudes of the Andes (especially Peru and Bolivia).

Polycytosis.—An increase in the cells of the blood both erythrocytes and leucocytes is characteristic of cholera.

Pulmonary.—We have included as pulmonary symptoms of tropical diseases those due to involvement of the lung as the result of direct invasion by the infecting organism as in pneumonic plague, as well as those regarded as secondary to invasion of the structures as in malaria and relapsing fever.

Ancylostomiasis.—In hookworm disease cough and bronchitis have been reported and it seems probable that such manifestations may be connected with the course of the larvae through the pulmonary passages to reach the intestinal tract.

Bronchial Spirochaetosis.—There is a condition which more or less resembles lobar pneumonia, even to rusty sputum, but without signs of consolidation, and with negative roentgenograms, when we find spirochaetes in the sputum. In another type of bronchial spirochaetosis, the clinical picture is more that of pulmonary tuberculosis. There is a question whether these spirochaetes are causative or only secondary or accidental.

Filariasis.—The filarial embryos of *W. bancrofti* remain in the lung capillaries during the day and such embryos have been found in blood coughed up from the lungs.

Guha.—In Guam there is also a rather fatal capillary bronchitis affecting young children which goes under the name of epidemic asthma or, as termed by the natives, guha. This affection comes on during the rainy season and is attended with marked dyspnoea and slight elevation of temperature.

Heat Stroke.—Cheyne-Stokes respiration and pulmonary oedema are often observed in heat stroke.

Japanese river fever often shows bronchial involvement and cough at the time of the height of the fever.

Katayama disease may show a localized bronchitis early in the attack and from its rapid appearance and disappearance would seem to be a sort of patchy pulmonary oedema. This is connected with the passage of the larvae through the lungs. A similar bronchitis has been observed in infection with *Schistosoma haematobium* in Africa and *S. mansoni* in the West Indies.

Liver Abscess.—In liver abscess the crepitation at the base of the right lung, following congestion incident to the abscess of the right lobe of the liver, is of value in diagnosis. Rupture of a liver abscess into the lung occurs in about 10% of untreated cases.

Malaria.—In malaria we have a slight bronchitis in the ordinary types and some recognize a pulmonary type of pernicious malaria.

Monilia Infections.—Cases have been reported where a phthisis-like condition was due to a mould infection (*Monilia*). While such a condition may be primary it is more often secondary in cachexias, as may be the case with buccal *Monilia* infections (thrush) which occur in the victims of cachectic states.

Plague.—Plague pneumonia is characterized by profound prostration in a patient whose physical signs often do not seem to justify such extreme illness. The rather abundant and watery sputum soon becomes sanguinolent. Herpes labialis is absent. Besides primary plague pneumonia which develops directly from contact with a former case we have a secondary pneumonia which develops in the course of a typical case of bubonic plague as a metastatic phenomenon.

Relapsing Fever.—In relapsing fever there is frequently a moderate bronchitis at the time of the first febrile accession.

Typhus Fever.—Bronchopneumonia is probably the most common complication of typhus fever.

Undulant Fever.—This disease tends to show a bronchial involvement about the twelfth day of the disease. Crepitant râles, a moderate cough and slight dyspnoea may be noted. It was the presence of pulmonary signs along with the profuse sweating and anaemia of the disease that justified the designation Mediterranean phthisis.

Pulse.—In yellow fever a markedly slow pulse, between 40 and 50 is often recorded about the time of the remission (3rd or 4th day).

Queckenstedt Test.—This test consists of lumbar puncture, with the needle connected to a manometer for recording the intraspinal pressure. After noting the pressure the internal jugular veins are compressed to produce a cerebral congestion. Immediately the pressure of the intracranial fluid is raised and produces an increased pressure of the intraspinal fluid. This elevation is noted by a sudden rise in level of the fluid in the manometer, and is followed by a sudden decline on releasing the jugulars. Any serious narrowing of the spinal canal between the cranium and the point of the needle will cause the fluid level to rise more sluggishly, and the decline will likewise be slower than normal. In the event the canal is completely closed, the compression of the jugulars will not affect the level of the fluid in the manometer. This test is especially valuable in confirming the presence or absence of obstruction or narrowing of the lumen of the spinal canal. It is indicated when one suspects cerebrospinal block, syringomyelia, fracture or dislocation of spine, spinal tumor or any condition which may cause serious narrowing of the spinal canal.

Rat Bite Fever.—The following points should be looked for: (1) Sudden onset with chill. (2) The breaking down of a previously healed wound or inflammation surrounding a cicatrix from 6 to 8 weeks old. (3) Lymphangitis and lymphadenopathy. (4) Spirilla in the blood. For definite diagnosis the inoculation of a guinea pig may be necessary to demonstrate the Spirillum.

Reflexes, Altered.—Diseases in which altered reflexes and motor disturbances are of diagnostic value are included under this heading. Differential diagnostic data in regard to sensory disturbances when accompanied by altered reflexes are included.

Beriberi.—It is usually stated that the tendon reflexes of the lower extremity, especially the patellar reflex, are absent. While this is generally true they may at first show an exaggeration and some cases do not seem to show any decided change. There may be striking variation from day to day in the reflexes. The superficial reflexes, especially the cremasteric, are as a rule more active than normally.

The sensory changes in beriberi are less marked than those of the motor side. There is rarely complete anaesthesia but rather a blunting of sensation. Hyperaesthesia, particularly of the muscles of the calf of the leg, is well marked when the muscles are grasped with the hand.

The anaesthesia is earliest noted over the shin bone and dorsum of the foot. A loss of tactile sense is often noted about finger tips making it difficult for the patient to button his coat. The most striking motor phenomena are the foot and wrist-drop, especially the former. The extensor muscles are more markedly involved than the flexors. There is marked muscular weakness of the foot as well as the hands. The weakness of the muscles of the leg is often the first symptom to be complained of. The type of palsy in beriberi is mainly paraplegic although hemiplegic and monoplegic types have been reported. The paralysis of the diaphragm is the most serious of the muscle palsies.

Contractures of the muscles of the foot or calf of the leg may occur. Contractures of the muscles of the upper extremity are more rare. Muscular atrophy of the leg muscles is often marked. In the upper extremity the muscles of the hand are most frequently atrophied.

Kubisagari.—See paralytic vertigo below.

Lathryism.—In lathryism we have spasticity and an exaggeration of the reflexes.

Leprosy.—The usual statement is that there is an exaggeration of the deep reflexes. Ankle clonus has been rarely reported.

Anaesthesia is the most important symptom in the diagnosis of leprosy. This loss of sensation is often for pain and temperature with retention of tactile sense (dissociation of sensation—a prominent symptom of syringomyelia). The anaesthesia is not only found in the spots but associated with the leprous neuritis which chiefly involves the ulnar, facial and peroneal nerves. Muscle palsies and atrophies are common and the main-en-griffe appearance of the hand is seen.

Paralytic Vertigo.—A very remarkable disease called kubisagari or paralytic vertigo has been observed in Japan. This disease is thought to affect those living in stables. The attacks only last a few minutes and at other times the patient seems normal. During an attack there is ptosis and diplopia, speech disturbances and palsy of the muscles of the back of the neck, causing the head to fall forward. There may also be some paresis of the muscles of the extremities. The disease is not fatal. Cases have been observed in Switzerland.

Pellagra.—There is considerable variation from time to time in the reflexes. Some authorities attach diagnostic value to the appearance of an exaggerated reflex on one side and a diminution or absence of the corresponding reflex on the other side. Ankle clonus may be present. Paraesthesias and in particular a burning sensation of the erythematous areas are often noted. Hyperaesthesia of the dorsal and lumbar regions is often noted. Pruritus is at times complained of in the region of the perineum. There is generally muscular weakness.

Sleeping Sickness.—The deep reflexes are usually exaggerated and the superficial ones diminished or absent.

There is no distinct alteration of motor or sensory function except that of deep hyperaesthesia (Kérandel's sign). There is usually marked weakness of the muscles of locomotion.

Relapsing Fever.—(1) Sudden onset with rapid rise of temperature to 104 or 105°F. (2) Bilious vomiting. (3) Leucocytosis. (4) Remissions of 3 or 4 days followed by a second, third or additional pyrexial periods.

Rocky Mountain Spotted Fever.—See typhus.

Schistosomiasis.—In both rectal schistosomiasis and Japanese schistosomiasis there may be fever, eosinophilia and urticarial rashes as early manifestations. The same phenomena may characterize the onset of the vesical form (due to *S. haematobium*) of this group of helminthic infections. Cystitis and vesical calculus are the symptoms which particularly characterize the latter infection, while dysenteric manifestations are often associated with the rectal fluke. Particularly the schistosome infections of Japan and China may lead finally to cirrhosis of the liver, ascites and a terminal cachexia. *Schistosoma haematobium* may give rise to Egyptian splenomegaly.

Scrotum.—The following conditions are frequently found in the tropics: (1) Hydrocele of the tunica vaginalis. (2) Lymph scrotum from *Filaria.* (3) Boils. (4) Syphilis. (5) Malignancy. The examiner should prove that the swelling is not due to hernia in every case.

Hydrocele.—The tunica vaginalis may become distended with fluid. Except in cases of thick wall hydrocele they are translucent, while a haematocele is not. All hydroceles fluctuate. Filarial infections of the tunica are not rare. Such a condition is called chylous hydrocele.

Skin, Lesions of.—Ringworm infections of the skin are so common in the tropics that one should always make an examination for the causative fungi when doubt as to the nature of the lesion exists. Another point is that many hyperaemias, incident to other diseases, seem to furnish a favorable soil for fungi; thus, not infrequently Stitt found abundant spores and mycelial structures in scraping from the erythema of the early syphilitic secondaries. Again pruritic lesions may become infected with fungi as the result of scratching, which scratching may not only have this result but furthermore may obscure the dermatological characteristics of the primary disease.

Ancylostomiasis.—In ancylostomiasis the site of entrance of the infecting stage of the larvae is marked by a dermatitis—ground itch.

Dengue.—The true eruption of dengue is the one that appears about the fourth or fifth day as a measles-like eruption, starting about the wrists or ankles.

Dermatitis Due to Schistosomes.—Cort (1928) reports a number of cases of dermatitis of a papular to pustular nature, occurring in the state of Michigan (U. S. A.), produced by penetration of the skin by schistosome cercariae, *Cercaria alvea.*

This form of dermatitis is common in other localities. See p. 1433.

Epidemic Dropsy.—It has been a question, whether such a disease as epidemic dropsy is distinct from beriberi. An erythematous eruption about the face and a macular one of the trunk and extremities are usually stated to be features of this disease. See p. 1018.

Filariasis.—The cutaneous manifestations of filariasis include (1) the bleb-like lesion which disclose when the guinea worm is about to pierce the skin, (2) the Calabar swellings produced by *Ioa loa*, (3) elephantiasis and lymph scrotum and filarial abscesses due to *W. bancrofti*. *O. volvulus* (or *caecutiens*) gives rise to nodules or tumors on the sides of the chest, about joints, or on the back or scalp. They are usually quite superficial, with the skin freely movable over them.

Juxta-articular Nodes.—This is a condition in which small tumors form under the skin especially in the region of the elbows. These bean to walnut-sized tumors of the subcutaneous tissues may also be noted about the knees. A fungus has been reported as the cause but the present view is that the condition is generally a sequel of yaws.

Kala-azar.—There is a darkening of the colored skin of the natives suffering from this disease and it is to this feature that the disease owes its name (Black sickness).

In Europeans the appearance is more that one sees in old malarial cachectics, an earthy-gray color. The characteristics of cutaneous leishmaniasis are discussed under that heading.

Oriental Sore is especially common in Asiatic Turkey and Northern Africa. It begins as a small papule which eventually ulcerates, the sore scabbing over from time to time and again breaking down. Indolent granulations and a very protracted course are rather characteristic features. It is due to *Leishmania tropica.*

Leishmaniasis.—The most important point of differentiation of American leishmaniasis from oriental sore is the occurrence of ulcerating lesions of the mucous membranes of mouth or nose subsequent to the appearance of the oriental sore-like lesions on forearm, legs, trunk, or rarely the face. In Peru the term *uta* more properly belongs to the skin affections while *espundia* is the designation applied to the lesions of the mucous membranes. It may be stated that a form of oriental sore has been reported from Greece where mucous membrane ulcerations have been associated with the ordinary skin-type lesion.

Brahmachari has described a form of generalized cutaneous leishmaniasis, bearing a superficial resemblance to leprosy, which may develop, a variable number of months after apparent cure of kala-azar by antimony. Having found leishmania bodies in the lesions, he conjectured that some of the parasites survive the action of the drug, but with their virulence so attenuated that they can give rise only to a milder disease, a variant of cutaneous leishmaniasis, to which he gives the name "dermal leishmanoid," see p. 270.

Leprosy.—In nodular leprosy there may be the appearance of macules of greatly varying size and shape with a tendency sooner or later to symmetry. They tend to appear and recur in association with febrile accessions and, even when they have become permanent spots, they show increased redness, infiltration and tension when there is fever. The color is rather that of a sunburn and may be uniform or the center may be pale with copper-colored periphery. These spots appear by preference on face, backs of hands, buttocks, extensor surfaces of extremities and back. They may mark the location of later developing nodules. At first they are oily rather than scaly. Soon there is noted a disappearance of hair within the spot. These spots soon tend to become anaesthetic. The tubercles of leprosy are usually of a reddish-brown color.

In nerve leprosy the spots tend to appear on parts of the body usually covered by clothing, as scapular region shoulders, arms, thighs or buttocks. The outline is ovoid

rather than round and the spots may at first be hyperaesthetic rather than anaesthetic, as they later tend to become. In circinate eruptions there is often noted a pale center with brownish-red borders. These borders may be hyperaesthetic while the centers show anesthesia. Bilateral symmetry is more common in this than in nodular leprosy. Besides the spots nerve leprosy may show blister-like lesions on the backs of hands and feet especially in the region of the knuckles. Ulceration may follow.

Malaria.—Herpes is more common in benign types than in malignant ones. Urticaria is next in frequency. Malaria has seemed to be the cause of certain cases of purpura simplex.

In attributing skin manifestations to malaria one must always have in mind the scarlatiniform, urticarial and erythematous rashes that may be due to quinine and arsphenamine. Toxic rashes with fatal results also occur from sulfanilamide and sulfathiazole.

Pellagra.—In no other general disease is the skin eruption of such importance in diagnosis and it is practically impossible to make a sure diagnosis of pellagra in the absence of an eruption or the history of an eruption. The eruption tends to show itself in the spring but may first appear in the early fall. The lesions resemble a sunburn and burn instead of itch. The characteristics of the eruption are bilateral symmetry and sharp delimitation from the sound skin.

As a rule the lesions are dry and atrophic but more rarely, and usually in severe cases, the eruption may be moist and oedematous. The backs of the hands are the most common sites for the eruption but frequently there is an extension up the forearm. The neck, the bridge and alae of the nose, the region back of the ears and the front of the chest are often involved. In children the feet and legs are frequently involved. Scrotal eruptions are early manifestations.

Plague.—Very rarely cases of bubonic plague may show a small vesicle marking the site of the flea bite. Areas of necrosis of the skin, which are really sloughing patches, and incorrectly designated "carbuncles," may be noted, especially over the site of the buboes. In the later stages haemorrhages into the skin (petechiae) are common.

Prickly Heat.—This condition is extremely common in the tropics and the scratching to relieve the itching often leads to infection with fungi or pyogenic cocci.

Rat Bite Disease.—An eruption of purplish spots may accompany the fever. There may be a resemblance to erythema multiforme.

Trypanosomiasis.—Patchy areas of erythema are often noted in Europeans affected with this disease. These are frequently circinate with fading in the center and tend to appear on the trunk.

Tsutsugamushi.—A small necrotic ulcer with a dusky red areola, often located in the armpits or region of the genitals, marks the site of the bite of the infecting mite. From it a lymphangitis leads to the swollen glands. About the seventh day a macular eruption, which never becomes petechial, appears on face, then on trunk and extremities.

Tularaemia.—There is often a local lesion at the site of the bite of the infecting *Chrysops.* The tributary glands are swollen.

Typhus Fever.—Gangrene is particularly a feature of spotted fever of the Rocky Mountains and typhus fever, chiefly of the scrotum and prepuce with the former and of the extremities in the latter. In typhus there is a macular eruption which becomes petechial.

Urticarial Fever.—In Japanese schistosomiasis often the earliest symptoms are the urticarial rash and fever.

Skin, Pigmentation of.—It is well to bear in mind that the normal skin pigmentation in the negro race is black and that true pathological skin pigmentation as in Addison's disease will therefore be black and not bronze. Stitt has observed light colored members of the negro race become glossy black due to tuberculous Addison's disease. The gums and buccal mucosa of the negro normally have a bluish tinge and in healthy persons of negro ancestry there may be such a buccal pigmentation. The first step in determining the cause of skin pigmentation is to determine by the van den Bergh test if the color is due to an excess of serum bilirubin. This is a rapid diagnostic aid and differentiates the skin pigmentations due to serum bilirubinaemia from those produced by other causes. The main causes of skin pigmentation are pellagra, arsenic therapy, syphilo-

Sprue gives rise to a flatulent dyspepsia with gaseous eructations. In sprue there is often a raw sensation in the oesophagus, so that swallowing is painful.

Strongyloides.—See diarrhoea.

Syphilis, Hereditary.—A syphilitic child is never born of a non-syphilitic mother. A syphilitic mother however may give birth to a non-syphilitic child.

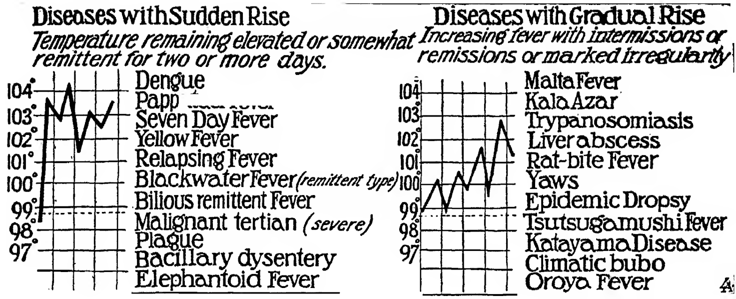

FIG. 396.—General type of fever onset in the various tropical diseases.

Temperature.—While a knowledge of the variations in type and course of the body temperature in the various tropical diseases may be of great value in diagnosis, yet such information is liable to lead one astray, unless such data are controlled by a careful consideration of the other and more important factors of physical diagnosis and laboratory examinations.

The idea that there is a scientific exactness in the employment of the clinical thermometer tends to make one overestimate its value in diagnosis. It must be remembered that the high air temperature one encounters in the tropics affects the clinical thermometer, which is of the maximum type. This is particularly true when the sun may be shining on the container in which the thermometer may be kept. Even if one shakes down the column of mercury before putting it in the mouth, the warm glass of the instrument will quickly cause the mercury column again to rise. It should be a practice to place the instrument in cool water before inserting it in the mouth and we must not forget that a sufficient retention in the mouth, from two to five minutes, may be necessary in some cases to assure a reliable temperature record.

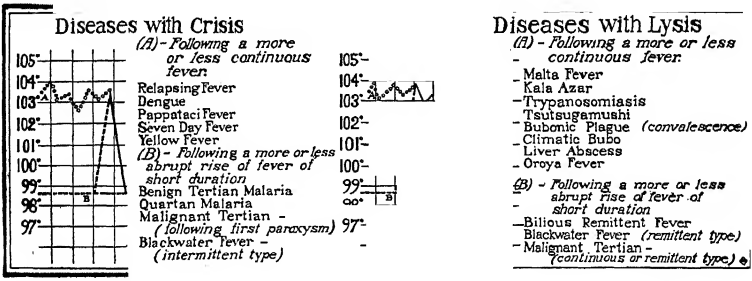

FIG. 397.—General type of termination of the febrile course in the various tropical diseases.

For practical purposes we may divide tropical diseases, from a standpoint of body temperature, into two classes. (1) *Those diseases in which the absence of fever in the general course of the illness is the rule, and* (2) *those diseases in which the presence of fever in the general course of the illness is the rule.*

The diseases in which the presence of fever, in the general course of the illness, is the rule, may be considered in two groups: (1) Those in which the temperature chart is

of prime importance in diagnosis. (2) Those in which the character of the fever gives but little assistance in diagnosis.

Diseases with Sudden Onset and Terminating by Crisis

Blackwater Fever.—The onset is usually quite sudden with a rather severe chill and marked lumbar pain. The temperature rises rapidly about 104°F. and may fall in a few hours to a point but little above normal accompanied by profuse sweating. The fall in temperature is not followed by a feeling of improvement. On the other hand there may be a fever course of remittent or even continuous type. That which is most characteristic and which in the majority of cases enables the patient to make his own diagnosis is the passage of dark or porter-colored urine.

The urinary sediment is simply granular débris, there are no intact red cells. It is a haemoglobinuria and not a haematuria. If there is any blood in the urine in yellow fever it is in the form of a haematuria. The urine in both blackwater fever and yellow fever is highly albuminous. In some cases the haemoglobinuria seems to result from quinine administration alone, in which case there is not the high fever of typical blackwater fever. As distinguishing it from yellow fever we have a marked jaundice which comes on in a few hours or even with the first appearance of haemoglobinuria instead of being delayed until the third day, as in yellow fever. Again, the blackwater paroxysm is intensely prostrating, it is markedly asthenic, while the onset of yellow fever is quite sthenic in character. The enlarged tender spleen of blackwater fever is also a prominent feature, which is absent in yellow fever. Bilious vomiting is an early and severe feature of blackwater fever but not the black vomit of yellow fever which does not come on until after the third day.

The jaundice of bilious remittent fever does not appear before the second day and the urine shows bile pigments instead of haemoglobin.

Dengue.—In this disease the extremely sudden onset with a fever rising rapidly to 104°F. or more and remaining elevated for three or five days, to fall by crisis to normal and, after an apyrexial period of one or two days, to be succeeded by a second febrile accession, gives a fever chart which is quite characteristic—the saddle-back chart. The typical dengue eruption does not appear until towards the end of the primary fever or about the commencement of the secondary one. Intense postorbital soreness is a striking feature in dengue. The comparative slowness of the pulse may be noted in dengue as well as in yellow fever. Leucopenia and polymorphonuclear percentage reduction are rather characteristic.

Malaria, Benign Tertian and Quartan.—The presence of a fever of tertian or quartan periodicity is absolutely characteristic of malaria. In rare cases however of meningococcus sepsis, without cerebral localization, we may have a tertian or even quartan periodicity. Such cases are apt to show petechial spots and blood cultures give the diagnosis. As the result of the introduction by infected mosquitoes, on successive days, of two generations of malarial parasites in benign tertian or of three generations in quartan malaria, a quotidian periodicity may obtain. Such a type of fever is observed in tuberculosis, liver abscess and various pyogenic infections. The rise of temperature in benign tertian and quartan malaria takes place in about one-half the cases somewhat early in the day, while the daily rise in tuberculosis, septic conditions and liver abscess is more apt to occur in the evening, the evening rise being almost the rule in such diseases. Hectic fevers generally show a less distinct cycle of chill, hot stage and sweating than do the benign malarial paroxysms. At the same time the enlarged spleen, presence of parasites in the peripheral circulation and response to quinine are diagnostic points in malaria which must always be thought of. When quinine administration has caused the parasites to be temporarily absent from the blood the increase of large mononuclears is very suggestive.

Malaria, Malignant Tertian.—While benign malarial infections are more common in temperate climates malignant tertian is the one which usually prevails in the tropics. The onset in malignant tertian is rather insidious so that the case may be suspected as one of typhoid fever. At the same time the first paroxysm is apt to show a tertian periodicity while subsequent ones, by only remitting, and not showing an intermis-

sion, give the temperature picture of a continued fever in which periodicity is not easily noted. A study of such a chart will probably show that the curve tends to approach normal every other day. The suggestion of periodicity is almost of as great value as the actual drop to normal in the intermission. The remittent or even continuous type of fever in malignant tertian tends to yield to an intermittent one after a week or more of such fever.

Very characteristic of malignant tertian parosysms is that they set in with chilly sensations rather than a frank chill. It is for this reason that the so-called "dumb chill" is recognized as more serious than the frank unmistakable chill. The main feature of malignant tertian paroxysms is the pronounced and prolonged hot stage, which frequently lasts from twenty to thirty-six hours and may run over into the rising temperature connected with the development of the succeeding generation of parasites.

The terms anticipation and postponement are frequently used to explain the drawn-out fever of this type of malaria. There is great irregularity in time of development so that we get the impression of completed cycle before the accepted forty-eight hours as shown by a rising temperature within thirty-six hours—anticipation; or, instead of showing indications of a completion of cycle in forty-eight hours the fever still keeps up—retardation. The descent of the fever curve is much more gradual than the rise at the onset of the paroxysm. The fine hair-like rings of the tropical parasite are the only schizont stages usually found in the peripheral blood. As the rings enlarge they fail to appear in the peripheral blood so that blood examination at such times will be negative. The finding of crescents is proof of a malignant tertian infection.

In view of the fact that one is likely to fail to find parasites just before or just after a paroxysm, search should particularly be made for the pigment-carrying phagocyte—the melaniferous leucocyte.

In certain of the pernicious manifestations of malignant tertian, especially the hyperpyrexial type of cerebral malaria, the temperature may reach a very high degree, 107°F. to 110°F., and it is often mistaken for sun stroke by one not familiar with the fact that so-called sun stroke is often only this fatal form of malaria.

In algid pernicious malaria the axillary and, in particular, the rectal temperature remain elevated even with a subnormal surface temperature.

The infection in latent malaria is most often a malignant tertian one. Such cases often develop paroxysms following surgical operations or at time of pregnancy or child-birth. Clark and others have noted the abundance of parasites in smears from the placenta taken at time of delivery when the peripheral blood showed few or no parasites. Such an examination is of enormous value in differentiating a malarial paroxysm from puerperal sepsis.

Rat Bite Disease.—Following a rather long incubation period of from six to eight weeks, during which time the bite has healed, we have a rather sudden invasion with high fever, 103° to 104°F., chill and at the same time inflammation of the site of the bite with lymphangitis and some swelling of tributary glands.

After two or three days of high fever we have a fall by crisis with profuse perspiration. The temperature remains normal for a few days during which time the local swelling and inflammation subside. The fever again comes on, frequently with an eruption, to later on disappear and reappear. At such times the fever course is irregular. There may be as many as 12 of these febrile accessions.

Relapsing Fevers.—These fevers, when there are three or more relapses, can perhaps be more easily diagnosed from the temperature chart alone than is the case with any other disease, excepting malarial fevers showing tertian or quartan periodicity. With an abrupt rise of temperature, which remains elevated for from three to seven days and drops by crisis to normal, to be followed by approximately a week of normal temperature, with two or three repetitions of the fever and apyretic intervals we have an extremely characteristic temperature chart.

Unlike malaria and yellow fever the onset is apt to be towards evening rather than in the early afternoon. The spleen is apt to be enlarged during the pyrexia and less so when the temperature is normal. The spirochaetes are to be searched for while fever is present as they disappear from the peripheral circulation during the apyretic intervals.

In tick fever numerous relapses are frequent in the European (or Caucasian) and less common in the native.

Yellow Fever.—With a sudden onset and rapidly rising fever, which often occurs in the early morning hours, in a patient who has gone to bed feeling well, there is a markedly congested face and neck with injected conjunctivae and intense headache and backache. The fever tends to remain elevated for about three days after which there may be noted a fall in temperature or even an intermission. This, which has been termed the period of calm, is often slight and of short duration. About this time the jaundice and haemorrhages show themselves and the temperature tends again to rise although less marked than with the sthenic fever of the first two or three days. Of great importance is the fact that the pulse rate falls with a maintained temperature or does not increase in rate as the temperature rises (Faget's sign). A very slow pulse is quite characteristic of yellow fever after the third day.

Important in the diagnosis of yellow fever from bilous remittent fever and blackwater fever is the absence of splenic enlargement in the former. In particular must it be remembered that jaundice does not show itself in yellow fever until about the third day, following which we may have bleeding from the gums and black vomit.

Melaena and haematuria may also be noted. The presence of a marked albuminuria is one of the leading characteristics of yellow fever.

Diseases with Gradual Onset and Terminating by Lysis

Kala-azar.—This disease has a peculiarly insidious onset because, with a fairly high remittent fever, it may cause but slight feeling of illness in the patient. Rogers insists upon the importance of taking the temperature every four hours so that one may note the fact of there being two distinct rises in the twenty-four hours instead of the single evening rise of typhoid fever.

At first it may be confused with malaria as well as typhoid. The spleen becomes greatly enlarged by the third or fourth month and later on we also have enlargement of the liver. Periods of fever and apyrexia occur irregularly and over a period of months or even longer than a year. There is a marked leucopenia and the presence of Leishmania, often in large numbers, in the juice from spleen or liver puncture, furnishes a certain diagnosis.

Liver Abscess.—In the so-called pre-suppurative stage of amoebic hepatitis the only symptom may be an irregular remittent fever of moderate degree. This and a leucocytosis may be the only points noted. In fully developed liver abscess we have a painful liver which is enlarged upward often with pain referred to the right shoulder and a crepitation at the base of the right lung. The fever is distinctly hectic in type with an evening rise and associated with profuse sweatings. The evening rise of temperature does not usually tend to exceed 102°F. and apyrexial intervals are frequently observed in the fever chart. It must be remembered that liver abscess has been found at autopsy where fever had not been noted. A sensation of chilliness often accompanies the evening rise of temperature.

Malta Fever. (Undulant Fever.)—In this disease, in which the wave-like febrile periods during every three or four weeks are so characteristic as to give it the name of "febris undulans," there is a very insidious onset. For a week or ten days the temperature climbs up stepladder-like and then descends in like manner to be followed by a few days of apyrexia with succeeding similar relapses. The case might suggest an attack of typhoid with relapses.

The course of the disease is attended by rather marked anaemia and physical and mental depression. Very characteristic are the fleeting joint pains which involve chiefly the knees, hip, ankle and shoulder joints. There are pain and some swelling but without redness. Neuralgic pains are also common. There is often a bronchitis which, when associated with the rather common night sweats of the disease, is suggestive of phthisis. The cardiac muscle seems to be especially liable to the toxic effects of the disease so that a weak heart and intermittent pulse are often noted. It has a very protracted course of, on the average, about four months

An astonishing fact is that so severe and prolonged a fever should give such a slight mortality (which in some series of cases has been only 2%). Occasionally, a case shows a high continued or remittent fever and aggravated symptoms, going into a typhoid state. Such cases may be fatal. There is an increase in the lymphocytes but no increase in total leucocytes.

The wave course of the fever, with afebrile intervals and increasing anaemia, is suggestive of kala-azar, particularly when there is a greater enlargement of the spleen than is usual in the disease. Ordinarily the splenic enlargement about corresponds to that of typhoid fever but at times it may be so much enlarged as to suggest the splenic tumor of kala-azar.

Oroya Fever.—This fever is regarded as the first stage of verruga, peruviana, which is characterized by a severe anaemia and invasion of the red cells with *Bartonella bacilliformis.* With pains of various joints and bones there is a gradual rise of temperature which after a few days reaches 103° to 104°F. and tends to become remittent or continuous. There is a remarkable and excessive destruction of the red cells which may fall to a million or less per c.mm. The fever after about three weeks begins to fall by lysis. Enlargement of liver, spleen and lymphatic glands are common. Pain over the bones, especially the sternum, is said to be often very severe. In the cases which recover, a verrucous eruption (the verruga stage) usually follows.

Trypanosomiasis, African.—The fever of trypanosomiasis is markedly irregular and may exist in natives without preventing them from carrying on their duties as porters. The onset is on the whole insidious. In this first stage of trypanosomiasis or trypanosome fever, when trypanosomes are found only in the glands and peripheral circulation, what may probably be considered as leading peculiarities of the fever are the great daily oscillations, a normal morning temperature being succeeded by an evening rise up to 102°F. or 104°F.

While the febrile course is usual in Europeans it is often absent in natives. With them the febrile manifestations are noted in the sleeping sickness stage. Again a very rapid, low tension pulse is present, whether the temperature be low or high. These febrile accessions are followed by apyrexial intervals.

Extremely important in diagnosis are the glandular enlargements of which those of the upper posterior cervical triangle are the most characteristic (Winterbottom's sign). Gland juice is more apt to contain trypanosomes than the film from the blood. Deep hyperaesthesia is also a very characteristic symptom (Kérandel's sign).

When the trypanosomes are found in the cerebrospinal fluid the disease has reached the second stage of trypanosomiasis or that of sleeping sickness. This is ushered in by a tremor of the tongue and mental symptoms of great apathy and listlessness. An irregular fever is present at times during the course of this stage of sleeping sickness but toward the end of the disease the temperature tends to be subnormal. Progressive weakness and emaciation with finally a comatose state are features of the terminal weeks.

Trypanosomiasis, South American.—The disease begins acutely in young children with an irregular remittent fever. The parasites are not apt to be found except during the fever. The lymphatic glands become swollen. With repeated accessions of fever, followed by apyrexial intervals, the child becomes weaker and more anaemic. The spleen is enlarged. This infection may be very fatal for children. In adults the disease tends to assume a chronic type. The disease has in some instances been associated with involvement of the thyroid, and symptoms of myxoedema.

Tsutsugamushi.—The disease sets in about a week after the bite of the Kedani mite with headache, chills and fever of about 101°F. There is also pain in certain lymphatic gland groups which will be found to drain the area in which is located a small necrotic ulcer, the site of the bite of the mite. The temperature continues to rise during the next two or three days to 104°–105°F. and remains as a high continuous fever for about a week, when an eruption of irregular dusky macules appears, first on the face and later on chest, extremities and trunk. About the tenth day the fever begins to go down by ysis and the eruption fades. Injection of the conjunctivae is marked.

There may be a striking clinical similarity to tsutsugamushi, Rocky Mountain spotted fever, and typhus fever. At present we recognize that all these and tabardillo, or Mexican typhus, are forms of Rickettsial infection.

Typhus Fever.—While the classical temperature chart is usually described as one with a rapid rise, reaching the maximum of 103° or 104° by the second day, with a fastigium of twelve to fourteen days, followed by a critical fall, yet many cases observed in the Balkans show a fairly gradual onset with a fall by lysis. A stuporous condition with, about the fifth day, a rash first appearing about abdomen and flanks, to soon become petechial, are important in diagnosis. There is a leucocytosis with marked acid staining of the granules of the polymorphonuclears.

Diseases in Which Fever Is an Important Feature but Gives Little Assistance in Diagnosis

Ancylostomiasis.—The occasional reports of fever being present have been perhaps connected with bacterial infection at the site of attachment of the hookworm in the intestinal wall.

Bacillary Dysentery.—The onset may be quite sudden and the temperature rise to 102°F. or 103°F. There is apt to be some evidence of toxaemia as shown by headache, slight flightiness and gastric disturbance. The dysenteric stool is of a reddish, mucopurulent appearance and flecked or streaked with blood rather than showing the uniformly brownish or greenish gelatinous material of amoebic dysentery. In very severe bacillary dysentery algidity may develop with a cold clammy skin, reminding one of cholera. At such times the temperature is subnormal.

Epidemic jaundice shows an irregular pyrexia of from 102° to 103°F. with jaundice about the second or third day.

Heat Stroke.—The onset may be as sudden as in apoplexy, although there are usually prodromata of dizziness and headache. The patient often is unconscious with dry burning skin, labored or stertorous breathing, and a temperature of from 107° to 111°F. The hyperpyrexial malarial paroxysm often presents much in common with heat stroke.

Intestinal Parasites.—There are many conditions which seem to be productive of febrile attacks as evidenced by the disappearance of the fever upon removing such cause. Thus patients presenting abdominal distress and a fever of varying type may be completely relieved of all symptoms upon evacuating the larvae of various flies following purgation. This condition is designated intestinal myiasis. Abdominal pains and fever may also be caused by various helminths formerly considered nonsymptom-producing, as has been noted in heavy *Ascaris* infections. The larvae, in wandering through the large capillaries may incite pneumonia.

Malarial Cachexia.—Attacks of an irregular type of fever are frequently noted in the malarial cachectic, especially arising after some exposure to dampness or chilling, to alcoholic excesses or to excessive fatigue. Cases are also met with in the tropics, particularly among natives, where there is no fever and yet profound anaemia and an ague-cake spleen. This absence of fever might suggest tolerance or evidence of immunity to malaria in the native with such anaemia and large spleen. Such cases often show crescents in their blood and act as reservoirs of virus for mosquito infection

Malaria, Latent.—Following treatment, or even when quinine has not been exhibited, cases of malaria, even though a cure has not been effected, often cease to show clinical symptoms or positive blood findings until a relapse develops. As noted elsewhere, these relapses, in which the febrile manifestations are prominent, often follow exposure to tropical sunlight, wetting, surgical operation, etc. Besides such frank manifestations, we may have numerous symptoms, that exhibit periodicity, arising in the course of nonfebrile latent malaria.

Plague.—The fever rapidly rises, so that the maximum temperature of 104°F. or more may be attained on the first day of the disease. In general the type of fever is continuous with a rather marked remission about the third day, following which, the fever usually again goes up with the appearance of the glandular involvement (bubonic plague). In fatal cases the temperature may rise rapidly just prior to death. The

alcoholic intoxication, and the early cardiac involvement, with very weak and irregular pulse, may suggest plague even before the buboes appear. Films and cultures from the buboes will furnish a definite diagnosis.

In plague pneumonia there is nothing characteristic about the rather continuous fever which sets in suddenly and continues elevated until death, which generally occurs about the third or fourth day. The marked mental involvement, the extreme illness of the patient, with but slight physical signs of the involvement of the lungs, should make one suspect a plague pneumonia urding an epidemic. The abundant, rather watery sputum, which later always becomes sanguineous, gives us a diagnosis by reason of its being loaded with bipolar stained plague bacilli. This material may be rubbed on the shaven abdomen of a guinea pig to make the diagnosis absolutely sure, the animal succumbing usually within three days to plague infection.

In septicaemic plague, if such be considered a distinct type, there is very little that is manifest except a fever in a profoundly ill person. The powers of resistance may be so overwhelmed that the temperature response is slight and the chart may not show temperature records above 100°F. or 101°F. Blood cultures furnish the diagnosis in septicaemic plague but in severe infections the plague bacillus sometimes may be seen in microscopical preparations of the blood.

Schistosomiasis.—In the vesical type of the disease we may have as a complication a pyelitis which could give rise to febrile manifestations. In Japanese schistosomiasis the disease may set in with fever and urticaria. Before this combination of symptoms was recognized as belonging to schistosomiasis it was sometimes designated "urticarial fever."

Spotted Fever of the Rocky Mountains.—In spotted fever of the Rocky Mountains the fever climbs up gradually for a week to reach its maximum and falls by lysis.

Trench Fever.—Cases of varying types of fever, some charts suggestive of dengue ones, but generally with repeated relapses, occur in trench fever.

In *tularaemia* there is an irregular fever course of rather rapid onset, extending over two or three weeks. There is very little evidence of toxaemia. Convalescence is tedious.

Typhoid fever and the *paratyphoid infections* are far from uncommon in the tropics and may sometimes present clinical courses at variance with those observed in temperate climates. The temperature charts in such cases are irregular and atypical. It must be remembered that paratyphoid infections may show marked gastrointestinal symptoms and that the rose rash of such cases tends to be far more profuse than that of typhoid.

Yaws.—While fever of a more or less irregular type frequently occurs at the onset of both primary and secondary stages, especially just before the secondary general eruption, yet the course of yaws as it runs over months or years is afebrile.

Diseases with Subnormal Temperatures

There are certain diseases in which marked lowering of the temperature may be a feature of some stage. The algid stage of cholera is that which gives to cholera the picture of a "living death" with the cadaveric features and icy breath. Again in the choleraic type of algid pernicious malaria we may have a subnormal temperature.

In severe infections of bacillary dysentery, we may have cases showing extreme toxaemia with algid manifestations and a subnormal temperature. During the last stages of sleeping sickness a lowering of the temperature is fairly constant. In heat prostration the temperature tends to be subnormal. Clinically this condition with its pale clammy skin is just the opposite of heat stroke with its turgid countenance and hyperpyrexia. In the Indian type of relapsing fever we may have a fall to subnormal temperatures at the time of the crisis of the first paroxysm, often attended with manifestations of collapse. Sprue cases tend to run a subnormal temperature during the terminal period.

Nonfebrile Diseases

Among the nonfebrile diseases we may note the following: Beriberi, sprue, pellagra, cholera, leprosy, amoebic dysentery, hookworm disease, filariasis, bilharziasis, endemic

haemoptysis or paragonomiasis, liver fluke disease, malarial cachexia, yaws, verruga, oriental sore and ulcerating granuloma of the pudenda, as well as the various tropica skin diseases.

One should always keep in mind the fact that a latent malaria often gives way to frank malarial manifestations when some intercurrent disease still further reduces the body resistance. This is not infrequently the explanation of a febrile onset in the course of a disease typically afebrile. In the tropics if a fever chart does not show a characteristic periodicity one can often obtain indications of periodicity even in a continued or remittent fever course by the greater elevation of temperature every third day (tertian periodicity). Another disease which often flares up, following conditions which lower vitality and gives rise to fever and manifestations of toxemia, is tuberculosis, a disease as common in the tropics as elsewhere. Then too, one must always keep in mind febrile manifestations not uncommonly marking syphilis. This triad of diseases, malaria, tuberculosis and syphilis, must always be thought of, as well as septic conditions, when fever is present in a disease typically afebrile. There are certain exceptions in the above list which may be here noted.

Amoebic Dysentery.—Unless complicated by hepatitis or some bacterial infection of the amoebic lesions the disease progresses without fever.

Beriberi.—There has been considerable discussion as to whether a disease with fever and a rash, but otherwise resembling wet beriberi, is the same disease or a distinct disease entity. The fever in epidemic dropsy, as it is called, is rarely over 102°F., usually ranging from 99° to 101° and accompanying the dropsy.

Cholera.—Instead of a favorable stage of reaction there may set in a condition with low muttering delirium, dry brown tongue and with an elevated temperature, the so-called typhoid state, which is speedily fatal.

Rarely a rise of 3 or 4 degrees which does not last more than forty-eight hours may be present in a stage of reaction going on to a favorable convalescence.

It must be remembered that the rectal temperature in the majority of cases of cholera may show elevation of temperature approximating 100°F., while the axillary temperature may be as low as 95°F. When there is a great difference between the rectal and axillary temperatures, instead of the more common 4 or 5 degrees of a typical case of cholera, the prognosis is bad. The temperature taken by mouth may be as low as 86°F.

Leprosy.—Among the prodromata of leprosy, along with epistaxis, feeling of great weakness, somnolence and occasional sweats, there may be recurring attacks of fever. These are at times diagnosed as malarial manifestations. With the appearance of typical lesions the course is apt to be nonfebrile with the exception that febrile accessions often accompany the early macular manifestations.

Pellagra.—While there may be slight variations from the normal yet the ordinary case of pellagra fails to show a distinct febrile course, so much so that the appearance of fever in a case of pellagra suggests an unfavorable prognosis. In the so-called typhoid pellagra, an acute, rapidly fatal form of the disease, a high temperature curve may be obtained. At the same time this condition has been noted by Italian and German writers as being present in patients not showing any rise in temperature. It is possible that the development of enteric fever in a pellagrin may at times be the explanation of the fever.

Sprue.—While sprue is certainly one of the most typical of afebrile diseases yet a form of sprue is recognized which begins as an acute entero-colitis with fever. This must be most exceptional, or only a coincidence, as sprue is characterized by a very insidious onset.

Tetanus.—History of wound one or two weeks previous; stiffness of neck; retraction of head. Convulsions with rigidity between contractions; opisthotonus; locking of jaws. Laboratory aids; make culture from wound; animal inoculation.

Trypanosomiasis.—Diagnostic features to be looked for: (1) Glandular enlargement of post cervical glands (See Winterbottom's sign). (2) Deep hyperaesthesia (See Kerandel's sign). (3) Lack of mental concentration, drowsiness or sleepiness. (4) Patient tends to sleep all the time. (5) Erythematous areas may be present. (6) Trypanosomes in gland juice, spinal fluid or blood.

South American Trypanosomiasis.—Acute type: (1) Usually in children. (2) Marked puffiness of face. (3) Enlargement of lymph glands and spleen. (4) High fever with morning remission. Diagnosis should be confirmed by laboratory procedures if possible. Such examinations should include microscopical examination of the blood for trypanosomes and the inoculation of guinea pigs with the blood. A complement fixation test has been employed. In the chronic form, symptoms of myxodema and enlarged thyroid have been reported. These symptoms may be due to an associated endemic goitre and are probably not dependent upon trypanosome infection.

Tsutsugamushi.—See typhus.

Tularaemia.—Tularaemia is a plague-like disease occurring in man following contact with rabbits or other rodents. Characteristic of tularaemia are: (1) History of contact with rabbits. (2) Local lesion on hands, head or eyes. (3) Followed later by sudden onset of fever and prostration. (4) Swelling and at times suppuration of lymph glands draining initial lesion. Animal inoculation and agglutination tests necessary for diagnosis. One not immune should not handle any animal inoculated with *P. tularense* without extreme caution and wearing of rubber gloves. It is apparently not transmitted from man to man.

Typhus Fever.—This louse-borne disease is characterized by a more rapid rise of fever and a more stuporous state than is true of typhoid fever, with which it was confused in the early years of the 19th century. The eruption appears from the fourth to seventh day, usually about the fourth day, and differs somewhat from the eruptions of spotted fever of the Rocky Mountains and tsutsugamushi. An important point in the diagnosis of typhus fever is the positive Weil-Felix reaction with Proteus X_{19}. The serum of Rocky Mountain spotted fever also agglutinates this strain, but the serum of tsutsugamushi cases does not. For differences in agglutination of these three diseases see p. 946. Another laboratory differentiation is the mild febrile affection noted in guinea-pigs inoculated with typhus blood while the animals infected with the virus of spotted fever of the Rocky Mountains show a very serious or fatal disease, frequently having necrotic lesions about the scrotum.

Ulcers.—Skin ulcers which vary greatly in etiology and symptomatology have been found in all parts of the tropics. One type has been described as tropical phagadaena or tropical ulcer. These ulcers are most frequently found on the dorsum of the foot, over the shin and about the external malleolus and, as in Veld sore, upon the face and hands. Syphilis undoubtedly is the cause of many ulcers, but in addition to this disease we must bear in mind also Veld sore, sickle cell anaemia, bacterial infections and ulcers of rat bite disease, etc. The finding of an inflamed cicatrix or the breaking down and sloughing of an old ulcer from six to eight weeks old with sudden onset of headache, nausea and weakness followed by swollen lymphatic glands draining the ulcer is characteristic of rat bite fever or tularaemia.

Leprosy.—In nerve leprosy we often have perforating ulcers of the feet and hands.

Sickle-cell Anaemia.—The ulcer of sickle-cell anaemia is multiple, punched out, indurated, occurs on the shin and is generally secondarily infected. In some cases there are pains in the bones and joints and osteoporosis may be demonstrated by X-rays. General glandular enlargement, negative Kahn and low blood pressure are found. The finding of the characteristic sickle shaped red blood cells (especially in sealed fresh preparations) is necessary for diagnosis. The disease is an hereditary constitutional anomaly practically limited to negroes, transmitted by either sex as a dominant mendelian characteristic.

Ulcers on the Face.—Syphilis, Delhi boil, glanders and blastomycosis should be particularly considered.

Ulcers in the Mouth.—Syphilis, pellagra, mercury poisoning, scurvy, sprue, pernicious anaemia, Vincents angina, pyorrhoea alveolaris, should be considered.

Undulant Fever.—The most significant finding in undulant fever is the characteristic temperature waves. Following the initial period of fever there is a short afebrile interval of a day or so to be succeeded by a second, third or many of these undulating waves, thereby giving to the condition its name. However, many cases do not show this type of fever. The symptom which may give the greatest aid to early diagnosis

is pain in the sacro-iliac region, with sudden and painful swellings of joints accompanied by enlargement of the spleen with anaemia and cardiac weakness. Blood culture and agglutination tests should be made to confirm the diagnosis.

Urobilinuria.—In conditions where there is a great destruction of red cells, tests for urobilin are important. Plehn considers the presence of urobilin as of importance in the diagnosis of latent malaria, which is true, provided other causes for red blood cell destruction are excluded. Blackwater fever cases usually show an intense urobilinuria. Urobilinuria is also a sign of deficient functioning of the liver.

Verruga.—Under the name Carrion's disease or Oroya fever there is a fever associated with rapidly occurring anaemia and bone pains and the presence of *Bartonella bacilliformis* in the blood. In the majority of the cases which recover, a verrucous eruption appears upon the skin. Strong, Tyzzer, and Sellards established the etiology of the febrile stage, while Noguchi and Battistini, who first cultivated *Bartonella bacilliformis*, showed it was also the cause of the verrucous stage of the disease as well and would produce the verrucous lesions in monkeys on inoculation. Townsend and Shannon have made studies of the puzzling epidemiology of the disease, which is restricted to endemic areas and can be contracted only by being in such a region at night, and after eliminating other blood sucking arthropods have incriminated two species of *Phlebotomus*, *P. verrucarum* and *P. noguchii*. These midges were collected in the endemic area of Peru, sent to New York and there, after being emulsified, were injected into the skin of rhesus monkeys. The organism of verruga (or Oroya fever) was cultured from the blood of these monkeys. See also work of Hertig, p. 1006.

Vomiting.—In yellow fever vomiting of bile stained mucus occurs early. Black vomit, if it appears, never comes on before the fourth day.

Weil's Disease.—See infectious jaundice.

Winterbottom's Sign.—Enlargement of the lymphatic glands, especially those of the posterior cervical triangle in trypanosomiasis.

Wrist Drop.—A paralysis of the extensor muscles of the hand and fingers is found in alcoholic neuritis, malaria, leprous neuritis, beriberi, poisoning from arsenic, lead and mercury. It may be due to trauma as in musculo-spiral nerve injury, or it may follow acute infectious fevers. Unilateral wrist drop is generally indicative of injury. See neuritis.

Yaws.—In many instances it would require the discriminating mind of a Jonathan Hutchinson to differentiate yaws from syphilis and in fact this greatest of diagnosticians said that, "if it were not syphilis it offered a very exact parallel." If we consider it as a modified form of innocent syphilis, contracted in childhood; with an environment of primitive culture and moist heat, we can understand its almost exclusive limitation to the tropics and to primitive people. An extragenital initial lesion of papular to condylomatous character is followed in 3 or 4 weeks by a generalized eruption of similar lesions. Fever, joint and bone pains, especially osteocopic, are common. Tertiary lesions similar to those of syphilis may occur, even aneurysm and cerebral haemorrhage have been reported in a few instances. Peculiar tertiary manifestations are: (1) Goundou, with a subperiostitis and enlargement of the nasal processes of the superior maxillary bones. (2) Gangosa, a destructive ulcerating process involving nasal and oral cavities. (3) Juxta-articular nodes, which are connective tissue tumours commonly located in relation to joints.

Yellow Fever.—The main points to consider in the diagnosis are: (1) Presence of vector and reservoir of infection. (2) Severe cephalalgia and rachalgia. (3) Albuminuria occurring on 2nd or 3rd day. (4) Epigastric tenderness. (5) Lack of correlation between pulse and temperature (see Faget's sign). (6) No clouding of intellect. (7) Late appearance of jaundice. (8) Tendency to haemorrhage, especially from gums, nose and intestines. See Chapter XXIII on yellow fever for differential diagnosis.

There is no quick test for the disease in the early stages but as Duff (1941) points out, the occurrence of cases with the foregoing syndrome in an endemic area often justifies the diagnosis and prompt application of local preventive measure.

Findlay (1941) believes the only certain diagnosis should be based on examination of liver tissue in fatal cases by a competent pathologist; mouse protection tests with the patient's serum both during fever and later during convalescence; and isolation of virus.

LABORATORY PROCEDURES USEFUL IN DIAGNOSIS, INDEXED BY DISEASES

This index has been compiled to assist in the selection of laboratory procedures which are likely to be of value in the diagnosis of the diseases listed, particularly those which can not be recognized by their clinical features alone. Only those of major importance in the tropics are given. The statements in the index apply to the average case, and many are subject to limitations or qualifications for which the text should be consulted. To be of value, laboratory tests must be performed with such precision that the probable technical error is well within the limits of the physiological variation. The results can be interpreted correctly only in conjunction with all the information available concerning the patient. This responsibility belongs to the clinician, and should not be expected of, or entrusted to a laboratory technician.

Abscess of Liver, Amoebic.—Aspirate contents aseptically and culture on blood agar plates (no growth unless secondarily infected). Pus resembles anchovy sauce. Stained films usually show detritus with few pus cells. Amoebae found in fresh preparations usually only after drainage has been established. Examine faeces for trophozoites and cysts. Moderate neutrophilic leucocytosis if acute. Monocytosis. Roentgenogram.

Abscess, Lung.—Sputum abundant, purulent, often foul; may layer on standing. Culture aerobically and anaerobically. Stain by Gram and Ziehl-Neelsen methods and examine *fresh* material for spirochaetes and fusiform bacilli, preferably with dark field. Look also for amoebae and for elastic fibres. Exploratory aspiration in some cases. Leucocytosis. Roentgenogram. Differentiate from tuberculosis, fungus infections ruptured liver abscess, tumor.

Abscess, Tuberculous.—If stained films of the pus are negative for pyogenic organisms, stain for acid-fast bacilli. Concentrate with alkali if necessary. Make cultures and inoculate a guinea pig. Leucocyte count variable. Sedimentation rate increased.

Acidosis.—If possible test CO_2 combining power of plasma. Alternatives: Test CO_2 tension of alveolar air. Measure titratable acidity + ammonia output in urine. Determine tolerance for $NaHCO_3$. Look for ketone bodies in urine. Test *p*H of urine. Ammonia in urine increased at expense of urea.

Actinomycosis.—Look for yellow "sulphur" granules in pus or sputum. Press out granules between slides and stain by Gram's method. The central mycelium is Gram-positive while peripheral "clubs" are Gram-negative. Culture anaerobically. (See p. 1183.)

Agranulocytoses (Malignant Neutropenia).—Leucopenia, becoming extreme, with disappearance of granulocytes. Red cells, platelets, coagulation factors usually normal. Granulocytes in marrow greatly reduced. Make blood culture to exclude sepsis. Stain films for Vincent's organisms. Differentiate from sepsis, acute leucopenic leukaemia and aplastic anaemia. Ascertain if drugs such as pyramidon or the sulfonamides have been ingested.

Allergy.—See Hypersensitiveness.

Amoebiasis.—Note gross and microscopic appearance of the stools. (See pp. 506–510.) Examine faeces for trophozoites and cysts. May show monocytosis. Differentiate from bacillary dysentery and chronic (non-specific) ulcerative colitis.

Anaemia, Aplastic.—Qualitative changes in red cells slight. No signs of regeneration. Marked neutrophilic leucopenia and thrombocytopenia with purpura. Sternal marrow shows few erythroblasts or myelocytes.

Anaemia, Haemolytic.—Positive indirect van den Bergh. High icterus index. Urobilin increased in urine and faeces. Reticulocytes usually increased. Leucocytosis. In fulminant cases look for haemoglobinuria.

Anaemia, Hypochromic.—Cells very pale, usually small. Color index and saturation index low. Corpuscular volume usually low. Icterus index normal or low.

Anaemia, Idiopathic Hypochromic.—Largely limited to women 20 to 50 years old. Usual features of hypochromic anaemias marked. Leucopenia frequent. Subacidity or achlorhydria, usually even after histamin. Reticulocyte crisis follows administra-

tion of large doses of iron. Differentiate from chronic post-haemorrhagic anaemia, chlorosis, cancer, hookworm anaemia.

Anaemia, Pernicious.—High volume index and high color index. Marked anisocytosis, macrocytosis, poikilocytosis. Megaloblasts in severe untreated cases. Evidences of haemolysis during progressive stages. Leucopenia with hypersegmented neutrophiles. Blood cholesterol reduced. Achlorhydria after histamin. Reticulocyte crisis follows administration of potent liver extract in severe cases.

Anaemia, Posthaemorrhagic, Acute.—Features of hypochromic anaemia present in moderate degree. Usually reticulocytosis, leucocytosis and increase in platelets. Normoblasts may appear after third day.

Anaemia, Posthaemorrhagic, Chronic.—Features of hypochromic anaemia marked. Low color and saturation index. Evidences of regeneration variable. In late stage may show aplastic type of anaemia.

Anaemia, Sickle Cell.—Seal fresh moist preparations and observe for 1 to 24 hours for sickled red cells. (Rare in stained films.) Severe cases show many normoblasts, reticulocytosis, leucocytosis, increased platelets. Look for macrophages containing red cells. Roentgenograms of skull may show changes. Limited to negroes.

Anaphylaxis.—See Hypersensitiveness.

Ancylostomiasis.—Examine faeces by concentration methods for characteristic ova. (See p. 1266.) Examine blood for anaemia (hypochromic, microcytic) and eosinophilia.

Angina, Streptococcal.—Make cultures on Löffler's serum and blood agar plates. Stain films with Löffler's methylene blue and Gram. Differentiate from diphtheria and Vincent's angina.

Angina, Vincent's.—See Fuso-spirochaetosis.

Anthrax.—(1) Malignant pustule. Examine material from pustule directly in stained films and hanging drop for large, Gram-positive, non-motile bacilli. Culture on agar. Inoculate a mouse or guinea pig subcutaneously. Blood cultures rarely positive. (2) Woolsorters' disease. Examine sputum in a similar way.

Ascaris Infection.—Examine faeces for characteristic ova. Worms occasionally found in faeces or vomitus.

Balantidium Infection.—Look for large motile ciliates in faeces.

Banti's Disease.—Moderate to severe anaemia, usually hypochromic in type. Leucopenia. Test fragility of the red cells to exclude haemolytic jaundice. Make van den Bergh test and determine icterus index. Test liver function. Examine faeces for occult blood.

Blackwater Fever.—Haemoglobinuria: pink foam to urine; test filtrate for haemoglobin spectroscopically and by benzidine or orthotolidine test. Malarial parasites found in thick blood films in some cases. Leucopenia. Monocytosis. Examine blood serum for haemoglobin and bilirubin (van den Bergh test). Donath-Landsteiner test negative.

Blastomycosis.—Examine sputum, pus, or scrapings from margins of ulcers in 10% KOH for spherical, budding yeast cells with highly refractile, double-contoured walls. Make culture on glucose agar plates.

Botulism.—Inject an infusion of the suspected food into a guinea pig. If positive animal dies after bulbar and papillary symptoms. Culture anaerobically on glucose agar. Culture may be kept in a dark place at room temperature.

Brucellosis.—Make blood culture at onset of febrile paroxysm; incubate in atmos phere of 10% CO_2. Make cultures from urine, faeces, and local foci in special cases. Guinea pig inoculation sometimes successful. After fifth day make agglutination tests; titer of 1–100 or over is diagnostic. Intradermal test with vaccine. Relative lymphocytosis, often leucopenia. Differentiate from typhoid fever, tuberculosis, malaria, kala azar.

Cerebrospinal Fever.—See Meningitis, meningococcus.

Cestode Infections.—Examine faeces for ova, which are not always present. If a segment is obtained, press between two glass slides and examine the branchings of the uterus.

Chancroid—Ducrey's Bacillus.—Examine smears for short, Gram-negative cocco-bacilli occurring in chains. Culture material aspirated from bubo, in sterile clotted human or rabbit blood which has been inactivated at 56°C. for 30 minutes. Syringe and media must be warm.

Chlorosis.—Hypochromic microcytic anaemia, sometimes severe, in adolescent girls. Low saturation index. Gastric acidity normal. Differentiate from chronic posthaemorrhagic anaemia.

Cholera.—Smears from flecks in rice-water stools show many vibrios with "fish in stream" arrangement. Culture on Dieudonné plates. If sparse, use enrichment method. Identify organism with cholera immune serum. After fourth day test serum for agglutinins. Intense dehydration with high blood counts, high plasma proteins and high specific gravity of blood. Anuria with high non-protein blood nitrogen. Acidosis from loss of base. Depletion of chlorides. Differentiate from food poisonings, arsenic or antimony poisoning, bacillary dysentery, algid pernicious malaria.

Chyluria.—Centrifuge urine and examine for filarial larvae. Examine blood at night for filarial larvae (not always present). Urine contains many highly refractile fat globules soluble in ether.

Cirrhosis of Liver.—Do Wassermann or Kahn test. Icterus index and van den Bergh test. Test urine for bilirubin and urobilin. Make tests of liver function and Takata-Ara test or determine A/G ratio. Examine faeces for occult blood. Late cases may show macrocytic anaemia. (See also Banti's disease, Liver, necrosis of.)

Coccidioidal Granuloma.—Examine pus or scrapings from ulcers in 10% KOH for large yeast-like cells which may contain endospores. Biopsy if necessary. Culture on glucose agar. Make blood culture. Exclude tuberculosis by repeated stains, cultures and guinea pig inoculation. (See p. 1153.)

Colitis, Chronic Ulcerative.—Examine faeces or preferably scrapings from ulcers (protoscope) for pus, blood, mucus. Exclude amoebic and bacillary dysentery by fresh warm-stage preparations, cultures and agglutination tests. Neutrophilic leucocytosis, often secondary anaemia, increased sedimentation rate. Roentgenograms.

Colitis, Mucous ("Spastic Colitis").—Examine faeces for mucus in large masses, containing epithelial cells, often eosinophiles, no pus cells, no blood. No leucocytosis, normal sedimentation rate. Roentgenograms.

Coma.—Examine urine for sugar, ketone bodies, albumin, casts, blood. Examine blood for sugar, CO_2 combining power, non-protein nitrogen or urea, and in special cases for alcohol and CO. Consider possibility of other poisons. Remove spinal fluid cautiously, examine especially for pressure, presence of red cells and xanthochromia (subarachnoid haemorrhage). Make leucocyte count and blood culture if febrile.

Conjunctivitis.—Stain smear by Gram's method and with dilute carbol fuchsin. Culture secretion on blood agar and plain agar. (See p. 1681.)

Dengue.—Neutrophilic leucopenia.

Dermatomycoses.—Examine scrapings from skin in 10% KOH for fungi. Culture on Sabouraud agar.

Diphtheria.—Make smears and cultures on Löffler's serum or whole egg medium. Stain by Gram's and Löffler's or Neisser's method. Look for parallel rods containing polar granules. In special cases isolate on tellurite blood agar and inject guinea pig with broth culture filtrate as test for virulence. Make Schick test on contacts. Differentiate from streptococcus and Vincent's infections.

Diphyllobothrium Infection.—Operculated ova in faeces. If segments are obtained, press one between two glass slides and look for characteristic rosette-shaped uterus. Macrocytic anaemia occurs in rare instances.

Dracunculus Infection.—Moisten blister or ulcer with a few cubic centimeters of water. Examine fluid excreted by worm for striated larvae.

Dysentery, Amoebic.—Examine mucus from fresh warm stool (warm stage) for amoebae actively putting forth blade-like pseudopodia. If necessary pass rectal tube, give saline purge, or scrape base of ulcer through a proctoscope. Pathogenic amoebae often contain red cells. Examine faeces for four-nucleated cysts. Smear of faeces shows granular detritus, often Charcot-Leyden crystals, no pus cells. Monocytosis. No eosinophilia.

Dysentery, Bacillary.—The sanguinolent mucus contains many pus cells and many phagocytic endothelial cells. Emulsify mucus in sterile broth or salt solution and plate on Teague, Endo or desoxycholate citrate medium. Identify organisms isolated by agglutination with immune sera. Neutrophilic leucocytosis. After 7 to 10 days make agglutination tests.

Echinococcus Disease.—Examine fluid from cyst for hooklets. Eosinophilia. Make complement fixation, precipitin, or cutaneous tests with special antigen. (See p. 1478.) Roentgenograms.

Elephantiasis.—See Filariasis.

Enteritis, Tuberculous.—Stain smear from faeces for acid-fast bacilli. There are often present in faeces acid-fast, spore-like bodies which should not be mistaken for tubercle bacilli. Tubercle bacilli may be present in faeces when there is no involvement of intestine (swallowed sputum, particularly in children).

Eosinophilia.—Look for ova of intestinal parasites in faeces. Look for evidence of trichinosis, hydatid disease, filariasis, various skin diseases, asthma and other allergic reactions, and lesions of the bone marrow.

Favus.—Place hair or portion of favus cup on a slide and examine in 10% KOH for mycelium and spores which are very irregular.

Filariasis.—Examine blood (day and night) for larvae, either in fresh moist preparation or better in thick films stained by Giemsa. (In elephantiasis larvae are often absent from blood.) Aspirate lymph varix or hydrocele and examine sediment for larvae. Examine sediment of chylous urine or ascitic fluid. Often eosinophilia. Complement fixation test sometimes positive with special antigen.

Flagellates, Intestinal.—Examine faeces emulsified in salt solution for motile flagellates. Emulsify another portion in Gram's solution to study flagella. Stain smear with Giemsa's stain for encysted forms, which may be confused with Blastocystis. (See pp. 463–470.)

Fusospirochaetosis (Vincent's Angina and Stomatitis).—Stain films of material from the depths of the lesion with dilute carbol fuchsin or Fontana's stain. (The spirochaetes and fusiform bacilli are present in large numbers; a few may be present in normal mouths.) Make cultures on Löffler's serum and blood agar to exclude diphtheria and streptococcal infection. Examine blood to exclude leukaemia and agranulocytic angina. There may be a marked lymphocytosis. Exclude syphilis by Wassermann or Kahn test. In pulmonary infections examine *perfectly fresh* sputum in stained films and dark-field preparations. See Abcess of lung.

Gas Gangrene.—(Infections are usually mixed; important organisms are *Cl. welchii*, *Cl. oedematiens* and *Cl. oedematis-maligni*. Precise identification difficult but important because of serum treatment.) Make hanging drop and stain smears from exudate by Gram and for capsules. (All are Gram-positive; *Cl. welchii* is encapsulated and non-motile; the other two are motile and non-encapsulated.) Make anaerobic cultures in litmus milk and glucose agar tubes. (*Cl. welchii* causes gas formation and disruption of the tube over night.) Blood cultures (anaerobic) may be positive.

Glanders.—Smears from pus show characteristic Gram-negative bacilli, parallel beaded rods. Culture on acid glycerin agar and potato. Inoculate male guinea pig intraperitoneally. (See p. 735.) Complement fixation and agglutination tests may be positive. (Mallein tests in animals.)

Gonococcus Infection.—Gram's stain of smear from urethra, cervical canal or eye shows intracellular, Gram-negative diplococci. Make culture. Complement fixation test useful in chronic infections.

Granuloma Venereum.—Stain scrapings from ulcers for Donovan bodies in large mononuclear cells (Wright or Giemsa).

Haematuria.—Examine sediment for red cells. Apply orthotolidine test.

Haematuria, Egyptian.—(See Schistosomiasis.)

Haemoglobinuria.—Examine centrifuged sediment for intact red cells. "Shadow cells" may be found with much debris. Test filtered urine for haemoglobin spectroscopically and by benzidine or orthotolidine test.

Hookworm Infection.—(See Ancylostomiasis.)

Measles.—A leucopenia with a coincident marked increase in the lymphocytes is characteristic of measles and occurs several days before the Koplik spots appear. The leucopenia and lymphocyte increase in measles are important points in differentiating it from scarlatina.

Pappataci Fever.—Leucopenia of 3000 to 2000 leucocytes is often present from the onset of fever and extends well into convalescence.

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Poisoning by Alcohol and Arsenic.—Chronic alcoholism and chronic arsenic poisoning cause a reduction in the number of the white cells.

Typhoid.—The leucopenia of typhoid is moderate and is often preceded in the first few days by a moderate neutrophile leucocytosis. Later on we have a decided increase in the lymphocytes. A marked diminution or absence of eosinophiles is so characteristic that any increase in eosinophilic percentage negatives a diagnosis of typhoid. Paratyphoid gives a similar blood picture.

X-ray treatment tends to destroy leucocytes in the exposed region, especially polymorphonu clears. The small lymphocytes are least affected.

Liver, Enlargement of.—It is well first to outline the upper edge of liver dullness by percussion; if it reaches much above the 5th right interspace in midclavicular line and the 7th interspace in the right midaxillary line it may be said to be enlarged upward. This is an important diagnostic point because the upward extension of liver dullness is rare and generally means, liver abscess, hydatid cyst or a subdiaphragmatic abscess. The lower border of the liver may usually be palpated in health as a firm smooth organ, rising and descending with the respiratory movement of the chest. Enlargement of the liver is usually downward. Three common causes of enlargement of the liver are, cardiac failure, cirrhosis and syphilis.

In the tropics one should keep in mind in addition to the above: (1) Abscess of the liver (more commonly found in the right lobe). (2) Tropical liver. (3) Malaria. (4) Relapsing fever. (5) Kala-azar. (6) Weil's disease. (7) Trypanosomiasis. (8) Malignancy of the liver (not uncommon). The less common causes are splenic anaemia, Hodgkin's disease, arsenic poisoning, carbon tetrachloride poisoning, leukaemia, cholangitis, amyloid disease of the liver and fatty infiltration and degeneration.

Kala-azar.—In kala-azar the liver does not begin to enlarge until after about three months from the time of onset at which time the spleen will be quite large. Decided enlargement is generally noted by the sixth month. Kala-azar patients are often carried off by a terminal pneumonia probalby connected with the leucopenia and marked diminution of polymorphonuclears.

Liver Abscess.—In liver abscess the enlargement is a rather late feature, and the condition should be diagnosed before we have the assistance of protruding ribs and distention of the intercostal spaces. As the abscess is usually located in the upper portion of the right lobe the enlargement is usually upwards and is best made out with the X-ray, showing the cupola-like projection.

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Liver Abscess.—In liver abscess, there are painful dragging sensations and, at times, with abscess of the upper right lobe, pain referred to the right shoulder. There is a marked tendency to splint the liver as shown by the costal breathing and moderate rigidity of the right rectus. The patient tends to lie on his back, as shifting to either side, especially the left, causes pain. The legs are drawn up to relieve tension. Any jolting of the liver in palpation is usually exquisitely painful. When active suppuration is going on in the liver the pain may be of an acute throbbing character. With abscess of the left lobe the pains may suggest gastric disease while with an abscess of the concave surface of the liver there may be referred pain in the appendix region.

Lunacy in the Tropics.—Van Loon, having examined over 200 cases from among 1100 insane patients in Java, found the most common types of mental disease to be

with leucin and tyrosin crystals, usually only after concentration. High non-protein nitrogen with low urea in blood. Hypoglycaemia. Decreased fibrinogen. Prolonged coagulation time. Decreased sedimentation rate. Acidosis may occur.

Lymphogranuloma Inguinale.—Frei test.

Madura Foot.—Discharge contains fish-roe granules which show mycelium and peripheral club-like structures.

Malaria.—Examine thin films stained by Giemsa or Wright's stain. If negative, stain thick films. To identify an object as a malarial parasite in stained films, one should be able to make out at least two of three characters: (1) chromatin; (2) bluish or greenish cytoplasm; and (3) pigment. Crescents are diagnostic for malignant tertian, equatorial banding for quartan. Marked irregularity of outline of parasite and the presence of Schüffner's (reddish) dots in cytoplasm of red cells suggests benign tertian. Leucopenia with monocytosis. Leucocytosis during the paroxysms. Anaemia of haemolytic type. Plasma globulin increased. About 15% show positive Wassermann reaction during febrile periods. May try provocative procedures. In special cases make sternal (or splenic) puncture. To test absorption of quinine, examine urine by Tanret's, Binz's or Andre's tests.

Meningitis, Meningococcus.—Blood cultures often positive in early cases and in simple meningococcaemia. Spinal fluid purulent, under high pressure. Culture *immediately* on warm blood agar. Examine stained film for Gram-negative intracellular or extracellular diplococci. Fluid gives a precipitin reaction with polyvalent anti-meningococcus serum. If cloudy fluid is obtained, it was formerly recommended to give serum immediately. However serum treatment is now generally not recommended. Circular 81 (Dec. 5, 1940) issued from the Office of the Surgeon General of the U.. S. Army recommends sulfanilamide, orally, as the drug of choice. Neutrophilic leucocytosis. Differentiate from septic meningitis, tuberculosis meningitis, poliomyelitis, encephalitis, benign lymphocytic choriomeningitis. Detect carriers by cultures from posterior nasopharynx.

Mercury Poisoning.—Examine urine or gastric contents for mercury. Examine urine for volume (oliguria), albumin, casts, renal epithelium. Determine blood non-protein nitrogen or urea, and creatinin. If severe, test for acidosis. Renal function tests show impairment.

Myxoedema.—Basal metabolic rate retarded (to −40%). Blood shows high cholesterol, low glucose. Low flat glucose tolerance curve. Anaemia, either macrocytic or hypochromic microcytic in type. Often lymphocytosis.

Nephritis, Acute and Chronic.—Examine urine, especially for albumin, casts, blood and pus cells. The presence of blood and red cell casts indicates an acute process. In acute cases look for streptococcal throat infections. Test renal function. Determine blood non-protein nitrogen or urea, and if high, creatinin or phosphorus. If impaired, determine blood chloride or bases, and test for acidosis. Anaemia common in advanced stages. (See "Nephrosis.")

"Nephrosis"—"Nephrotic" Stage of Glomerular Nephritis.—Examine urine: Oliguria, high fixed specific gravity, marked albuminuria, many casts, epithelial cells with doubly refractile fat droplets, pus cells, but few or no red cells. Chloride excretion reduced. Phthalein excretion normal. Blood cholesterol very high, plasma albumin reduced, A/G ratio inverted. Chlorides may be high. No nitrogen retention. Congo red test positive. Sedimentation rate much accelerated. Basal metabolic rate retarded. Anaemia common. Look for evidence of intercurrent infections.

Ocular Infection.—It is now recognized as advisable to make an examination for the *Pneumococcus* before performing operations on the eye as serious results may follow if the *Pneumococcus* be present. It is the organism most frequently responsible for infections after cataract operations. It is frequently found in dacryocystitis and, in the case of traumatism, may bring about panophthalmitis.

The *Pneumococcus* is a fairly common cause of serpiginous corneal ulcerations for which active treatment is necessary. Corneal ulcerations are not apt to appear even with a pneumococcal conjunctivitis unless there be an injury of the epithelium.

The pyocyaneus bacillus may cause severe purulent keratitis as well as conjunctivitis. The pyocyaneus toxin appears to be a factor in the production of the lesions observed.

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Demodex may cause an obstinate blepharitis.

For *xerophthalmia* and *night blindness*, due to deficiency of Vitamin A, see p. 1030.

Oedema.—Examine urine for evidence of nephritis. Test renal function. Determine plasma proteins, A/G ratio, blood chlorides.

Onchocerciasis.—Aspirate fluid from a nodule and look for motile larvae in fresh preparation, or stain by Giemsa. If negative, excise a nodule and look for adult worm or (very numerous) larvae. Clip off a bit of skin or conjunctiva, moisten in a few drops of salt solution and look for larvae. (Larvae are not present in the blood.) Complement fixation test usually unsatisfactory.

Ophthalmia Neonatorum.—(See Gonococcus Infections.)

Oriental Sore.—Examine scrapings from base of ulcer for Leishman-Donovan bodies. Stain with Wright or Giemsa. Preferably obtain material by aspiration by puncture near edge of ulcer. If bacterial contamination can be avoided, culture on NNN medium. In espundia obtain material also from adjacent lymph nodes by puncture

Oroya Fever.—Acute, rapidly developing haemolytic anaemia. Rod-like organism, *Bartonella bacilliformis*, in red cells.

Paragonimiasis.—Examine fresh sputum for light-yellow, operculated ova, averaging 90 by 65μ. Also for pus, blood, elastic fibres. Exclude tuberculosis.

Paratyphoid Fever.—Examine as for typhoid fever.

Piedra.—Examine hairs for small gritty masses which consist of spores arranged like mosaics about hairs.

Plague—Bubonic Type.—Examine material obtained by gland puncture for *P. pestis*. Stain smears, culture, and inoculate a guinea pig to identify. *Pneumonic type:* Examine the thin, watery, blood-tinged sputum in the same way. To obtain pure culture, inoculate on unbroken skin of animal. *Septicaemic type:* Make blood culture. *P. pestis* may be sufficiently numerous to be found in blood films. Leucocytosis. Differentiate from tularaemia.

Purpura Haemorrhagica (Thrombocytopenic).—Platelet count reduced. Bleeding time prolonged. Clot retraction impaired. Tourniquet test positive. Coagulation time usually normal. May show secondary posthaemorrhagic anaemia. Leucocyte count variable. See Onyalai p. 1133.

Rabies.—Keep dog, which has bitten patient, alive to observe symptoms. If dog has been killed, make smears from cornu Ammonis and stain by Giemsa's or Mann's stain for Negri bodies. (See p. 1603.)

Relapsing Fever.—Examine blood for spirochaetes with dark field or India ink method, or in smears stained by Wright's stain. (They may be absent from peripheral blood during afebrile period.) If not found, inoculate a mouse and examine its blood after 24 and 48 hours. Neutrophilic leucocytosis in acute cases. Differentiate from malaria, yellow fever, Weil's disease.

Rickets.—Blood phosphorus usually low, calcium normal. In some cases calcium is low and phosphorus normal. Product of Ca $\times$ P is below 40 and often below 30. Blood phosphatase increased. Examine blood for anaemia. Roentgenogram.

Rickettsial Infections.—Inoculate nearly-grown male guinea pig intraperitoneally with 1 cc. of blood obtained during febrile period. Take temperature of pig regularly and watch for febrile reaction after 5 to 12 days. Watch for swelling of scrotum, and examine scrapings from tunica vaginalis for Rickettsiae (Mooser bodies). Examine brain sections for small proliferative nodules and perivascular infiltrations. (See Table, p. 946.) Test serum of patient after 7 days for agglutinins for Proteus OX 19 (Weil-Felix). Moderate neutrophilic leucocytosis. (See also p. 946.)

Rocky Mountain Spotted Fever.—(See Rickettsial Infections.)

Scabies.—With the aid of a hand lens examine the infected skin for a black line which marks the tunnel for the parasite. The female can be found at the end of the tunnel and removed. If parasite is not found, look for ova in scrapings from skin.

Schistosomiasis.—Examine urine and faeces for ova, particularly in masses of blood-tinged mucus. Blood in urine. Examine blood for anaemia and eosinophilia. In late stages test liver function. Complement fixation reaction sometimes positive with special antigen.

Screw-worm Infection.—To identify, examine breathing slits on posterior stigmata of larvae found in auditory canal or skin ulcers.

Scurvy.—Tourniquet test of capillary resistance positive (as in purpura). Reduced excretion of cevitamic acid in the urine. May cause hypochromic anaemia.

Small Pox.—Initial leucopenia followed by neutrophilic leucocytosis in pustular stage. Monocytes increased. Try Paul's or McKinnon's corneal or skin, rabbit inoculation tests.

Sprue.—Examine the frothy, pultaceous stools for undigested food and excess fat (25% to 40%), chiefly fatty acids. Make gastric analysis (occasionally an achlorhydria). Examine blood for anaemia, usually macrocytic, like pernicious anaemia; occasionally hypochromic. Blood calcium reduced. Glucose tolerance curve has flat peak.

Sporotrichosis.—Culture on agar or potato for 8 days or more. Direct smears do not show organisms.

Syphilis.—*Primary stage:* Look for *T. pallidum* in serous exudate from chancre in dark-field preparations (or stained films). If negative, and ulcer is healing, examine juice aspirated from regional bubo.

Secondary, *tertiary* and *latent* cases: Make Wassermann reaction or flocculation tests. Examine spinal fluid if clinical evidence of disease of the nervous system is present; and in all cases before treatment is stopped.

Tetanus.—Inoculate white mouse or guinea pig and make anaerobic cultures from curettings from the wound. (See p. 1609.) Rarely found in smears. Inject filtrate from culture into two guinea pigs, one of which should be protected by injection of antitetanic serum.

Thrombocytopenia.—(See Purpura, thrombocytopenic.)

Thrush.—Make scrapings from lesions and examine in 10% KOH solution. The organism, *Syringospora albicans*, may be cultivated on Sabouraud's medium. It slowly liquefies gelatin and blood serum and acidifies and clots milk. In cultures there are budding yeast-like forms and mycelial threads.

Transfusion.—To select donor, secure individuals of the same blood group (or group O), and match the serum of the recipient with the cells of the donor and vice versa. Exclude syphilis by Wassermann or Kahn test and by physical examination. Exclude malaria by history and stained thick blood films.

Trichiniasis.—Usually high leucocytosis and eosinophilia. Secure suspected meat, examine for encysted larvae in press preparations, or digest in artificial gastric juice, and collect larvae in Baermann apparatus. (See p. 1243.) May feed meat to rat or mouse and examine muscles similarly after 10 days. During second or third week take 5 to 10 cc. of blood in dilute acetic acid and examine sediment for larvae. After second week excise a bit of muscle from deltoid or pectoralis near insertion and examine. Make intracutaneous test with Bachman antigen.

Trypanosomiasis.—Examine blood for trypanosomes in fresh preparations or stained thick films. When sparse, concentrate in blood by centrifugalization and make films from leucocyte layer. (See p. 191.) If not found, inoculate a rat or guinea pig intraperitoneally with blood, gland juice or emulsion of excised gland and examine blood at intervals. Formol-gel test often positive. In lethargic stage examine spinal fluid for parasites. Cell count and globulin increased. Differentiate from kala azar, malaria, syphilis.

Tuberculosis.—Make acid-fast stain of smears from sputum, faeces or urinary sediment. If necessary, first concentrate by digesting in alkali or antiformin and centrifugalizing. Culture on Petroff's medium or in Corper's medium. Inoculate guinea pig. Blood cultures may be positive in miliary tuberculosis. High monocyte-lymphocyte ratio indicates progressive lesion. Positive diazo-reaction in urine an unfavorable sign. In special cases make intracutaneous or subcutaneous tuberculin tests, or in children von Pirquet's cutaneous test. Sedimentation rate increased in proportion to activity of disease.

Tularaemia.—In the early stages inoculate mouse or guinea pig with material from local lesion or regional glands, or with blood. At autopsy look for characteristic lesions (small caseous foci in organs) and make cultures from blood and organs on glucose

cystin blood agar. After the first week test blood for agglutinins. Differentiate from Brucellosis, plague.

Typhoid Fever.—Neutrophilic leucopenia; relative lymphocytosis; eosinophiles reduced or absent. Blood culture usually positive during the first week, later less frequently obtained. Culture urine and faeces on Endo, Teague or bismuth sulphite medium. Make agglutination test after 7 to 10 days. In suspected carriers culture urine and faeces or duodenal contents. Differentiate from paratyphoid fever, brucellosis, malaria, typhus, miliary tuberculosis, liver abscess, kala azar.

Typhus Fever.—(See Rickettsial Diseases.)

Undulant Fever.—(See Brucellosis.)

Urinary Tract Infections.—Examine sediment immediately in hanging drop and in films stained by Gram. Collect specimen with sterile precautions or by catheter and culture on agar and blood agar plates. In special cases search for tubercle bacilli by stain and culture and confirm by guinea pig inoculation. Digest sediment in alkali if abundant or contaminated.

War Wounds.—Films stained by Gram should be examined and cultures prepared both for aerobic (and by the Novy jar) for anaerobic micro-organisms. The presence of the "gas bacillus" *Clostridium welchii* can be demonstrated by inoculating material into a tube of litmus milk, heating it to 80°C. for an hour, and incubating it anaerobically for 12 to 18 hours. If this organism is present the so-called "stormy fermentation" results. It is not produced by other anaerobes.

To obtain pure cultures, inoculate 3 or 4 cc. of the whey into the ear vein of a rabbit. After 5 minutes kill the rabbit and place the carcass in the incubator for 6 to 8 hours. The body should become distended with gas and the organism should be obtainable from the foamy liver or the heart blood (Welch-Nuttall test).

If serum therapy is to be used successfully in cases of gas gangrene it is necessary to determine speedily and precisely which of the anaerobic organisms are present, since different antitoxic sera are required for each. Merely to demonstrate the presence of *Cl. welchii* is not sufficient, since many cases show mixed infections with two or more anaerobes. Henry (1917) has suggested a method for a quick identification of the important saccharolytic anaerobes in wounds, *Cl. welchii*, *Cl. oedematis maligni*, and *Cl. oedematiens*. The material is inoculated into a cooked meat medium, and from this into a tube of milk. If the stormy fermentation occurs *Cl. welchii* is present. At the same time some of the culture is inoculated into two guinea pigs, one of which has received *Cl. oedematis maligni* and *Cl. welchii* antitoxin, and the other of which has received *Cl. oedematiens* and *Cl. welchii* antitoxin. If the first pig dies it indicates that some organism other than *Cl. oedematis maligni* and *Cl. welchii* is present, and this is most often the *Cl. oedematiens*. This assumption is confirmed if the second pig survives. If the second pig alone dies one may draw the same conclusions with respect to the *Cl. oedematis maligni*. If both pigs die either both of these organisms or some other anaerobes are probably present and identification must be made by cultural methods. (See also pp. 1621 and 1679.)

Yellow Fever.—Early neutrophilic leucocytosis which in a few days falls to normal or below. Increasing albuminuria with granular and epithelial casts from the first or second day. Oliguria or anuria in fatal cases. Bile pigments are present in blood and urine in increasing amounts from the second or third day. Inject blood of patient (during the first three days) intracerebrally into mice. Serum of cases after recovery shows life-long protective power. Differentiate from severe malaria, blackwater fever infectious jaundice, relapsing fever, dengue, influenza. (See also p. 1674.)

Section III

TROPICAL HYGIENE

Climatic Influences

Tropical Climate

Foreword.—In Hopkins' (1938) Treatise on Bioclimatics, Figure 35 (derived from Supan's temperature zones, Bartholomew's Physical Atlas, 1899, vol. III; Meteorology, pl. I) shows that the "heat equator," which represents the line of maximal mean annual temperature in the tropical zone, lies for the most part at a considerable distance north of the geographical equator. In Central America and Mexico it bends northward to about 5° above the Tropic of Cancer (which is at 23°N.) and in part of Africa it lies at 20°N. latitude. Analogous curves are found in the isotherms of 68°F. (20°C.) which delimit the zone of tropical heat on the north and on the south. The northern limit of this zone passes through the most southern part of the United States of America, through the Mediterranean Sea, to the north of Arabia and India, and through the southern part of China. The southern limit bends sharply northward along the western slopes of the Andes in South America, and to a less degree near the western coast of Africa; and it passes south of the central portion of Australia.

Life must adapt itself, however, not to climate in terms of averages, but to the fluctuations of weather which may be irregular, seasonal, monthly, or diurnal. Therefore, the classifications of climates in terms of average figures, whether for temperature, humidity rainfall or barometric pressure, are inadequate indications of the possible influences of a given climate upon man. Moreover, elevation above sea-level, the proximity of mountains or of oceans, ocean currents, and prevailing winds, modify local climatic conditions to such an extent that localities which are not far distant from each other may have very different climates.

For detailed information on climates, the reader may consult the larger works such as the "Handbuch der Klimatologie" by Köppen, Graz and Geiger (1938) or he may find all that he requires in Kendrew's little book "The Climates of the Continents" (1937), or in C. E. P. Brooks' "Climate" (1932). The "Climatic Maps of North America" (C. F. Brooks: 1936) show sea level isotherms and actual average temperatures for various months, the mean annual range of temperatures, the maximal and minimal temperatures, and similar data for barometric pressure, rainfall, snowfall, humidity, cloudiness and thunder storms.

Thornthwaite (1933) has published a brief classification and description of the climates of the world on a quantitative basis together with a climatic map in color. There is a dearth of useful books on medical climatology. "Climate and Acclimatization," 2d edition, 1938, by Castellani, contains much valuable information in concise form

The knowledge of the effects of climates upon man is so incomplete that an elaborate classification of tropical climates is not needed here. Tropical climates are of three principal types: the hot and dry; the hot and humid; and the wet-dry climates which are characterized by alternating seasons of drought and of heavy rainfall. The hot and dry climate produces desert or semi-arid conditions, under which the days are apt to be extremely hot and the nights to be cool or even cold. In the hot and humid tropics, on the other hand, extremely high temperatures do not occur and the nocturnal fall of temperature is slight. In such climates, the fluctuations of temperature between

night and day may not exceed 10°F. and the seasonal fluctuations are small. During a prolonged dry season, the desert type of climate is approached and, in the course of a long wet season, humidity increases and temperature tends to decrease. Some of the coastal climates are similarly modified by seasonal trade winds. The effects of the monsoons of India extend far inland. They bring with them rainfall and lower temperatures. The climates of small islands are especially equable. Temperatures tend to range higher in the interior of large land masses than on the coast, and mountain ranges may determine the distribution of rainfall. This is notably true in tropical South America where there is abundant rainfall east of the Andes and aridity on the western coastal plain.

The mean annual temperatures in the tropical belt in general, vary from 80°F. to 84°F. When there are clearly defined wet and dry seasons, the wet season is comparatively cool. Annual rainfall in the tropics is usually 40 inches or more. At Puerto Bello in Panama, 241 inches have frequently been recorded and in the Khasia Hills in Assam, it has reached 600 inches.

The summer temperatures in the north temperate zone are frequently higher for short periods than those encountered in the hot and humid tropics. Ill effects of climatic heat, therefore, are not limited to the tropical belt.

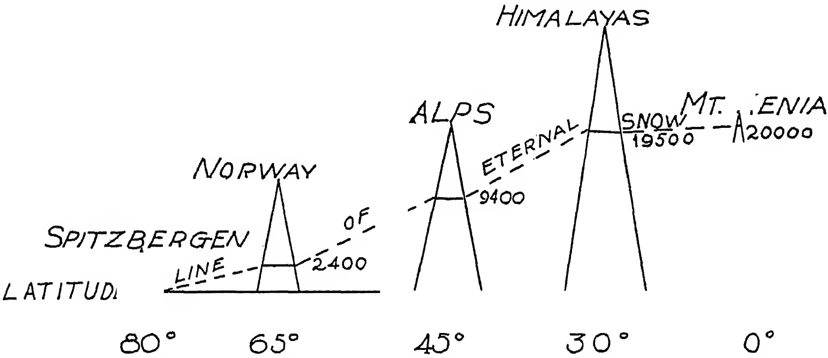

FIG. 398.—The relation of climate to altitude and latitude. (After Le Dantec from Hygeia.)

Mountain Climates.—Temperature varies inversely as the altitude. Herschel has shown that for every 300 feet of increase in altitude there was a decrease of 1°F. and for every 180 metres a decrease of 1°C. These statements are only partially correct however as the temperature at a given altitude depends in part upon the expansion and humidity of the air, the clearness of the atmosphere, the quantity of earth, and the nature of the wind blowing at the time. An interesting comparison showing that altitude has as much to do with climate as latitude is afforded by the annual mean temperatures for several places in the Island of Haiti. Port-au-Prince on the coast at approximately sea level has an annual mean temperature of 81°F. Petionville 4 miles inland with an elevation of about 1400 feet an annual mean temperature of 76°F. and Furcy 12 miles from the coast, at an altitude of about 5000 feet, an annual mean temperature of 66°F. Pine trees are found in the higher altitudes of the island. The highest altitudes of Mount Kenya, located at the equator about 300 miles from the east coast of Africa, are clothed in perpetual snow. North or south of the equator the snow line gradually descends until at about 80° north and south latitude it reaches sea level. This is shown in the accompanying chart from Le Dantec.

Important Climatic Elements and Their Effects in Brief

Heat, Humidity and Air Movement.—The climatic factor of principal importance in the tropics is heat. Climatic heat becomes particularly inimical to health when it

reaches levels which render difficult the dissipation of surplus heat from the human body. Lower levels of temperature may become inimical in this sense when heat dissipation is retarded by high relative humidity of the atmosphere or by the absence of air movement. Conversely, the effects of high temperatures are mitigated by low humidity or by air movement. These factors promote rapid evaporation from the skin and thus they increase the efficiency of this cooling mechanism.

It is useless, from the point of view of medical climatology, to discuss separately the effects upon man of heat, humidity and air movement. Attempts to assess climatic environment in terms of these factors will be dealt with on page 1690.

When, as a result of exposure to heat, the heat regulating mechanism of the body fails to prevent a considerable rise of temperature, heat pyrexia (p. 1085) results. When the circulatory mechanism fails to respond to the increased stress imposed by high temperature, heat exhaustion (p. 1090) develops. Heat cramps (p. 1091) are induced by excessive loss of sodium chloride in the sweat. Dehydration of the body is a factor which may aggravate the ill effects of heat. Schlegel (1941) has studied variations in the heat regulation of the human organism with particular reference to the water and salt losses caused by high temperatures. The experiments were conducted at a temperature approaching 40°C. (104°F.) and beneficial effects on the heat regulating mechanism were found to result from the administration of renal, cortical hormone. Under the influences of the hormone there was considerable increase in sweat loss. Six subjects were unable to continue the control experiments without hormone. Without hormone administration the pulse mounted rapidly but with hormone the pulse was steady, 80 to 90 throughout the experimental period. They thought this work indicated that acclimatization to a hot environment may be accelerated by the use of hormone.

Atmospheric Pressure.—Generally speaking, high pressure is recorded at sea level about 30 degrees north or south of the equator. This high pressure decreases towards the equator due to the heating of the air by the sun's rays and to the addition of aqueous vapor which, being lighter than the air, ascends with considerable force to very high altitudes. A normal man can frequently withstand a pressure of one additional or two absolute atmospheres in diving operations over a considerable period of time, and ascend to altitudes of over 15,000 feet without great difficulty. It is uncertain, however, whether the slighter variations of pressure are significant from the point of view of health.

Storms.—Local severe thunderstorms are frequent in the wet tropics. Generally, they cool the atmosphere for the time. Besides these, cyclonic storms which receive different names in various parts of the world occur at infrequent intervals. They are called cyclones in India and Mauritius, hurricanes in the West Indies, and typhoons in the West Pacific and contiguous seas. It is probable that hurricanes have been an important factor in the lack of progress of the white race in some of the islands, particularly of the Bahamas and West Indies.

Altitude.—Mankind can live and has established permanent habitations in Tibet at places over 4000 meters above sea level. In the Bolivian province of Chichus, people live at an altitude of 5000 meters. A moist tropical climate is the result of heavy rainfall, combined with low elevation while in tropical mountains with sufficient elevation, every variety of climate may be found. At Nairobi in Africa which is 3 degrees south of the equator but has an altitude of from 6000 to 8000 feet the climate varies from cool to cold in the higher elevations while hot tropical conditions prevail on the coast.

Altitude is important because of its effect in tempering the heat of the lowlands and in providing sites for sanatoria and rest camps for relief from the heat and humidity of the coastal plains. Baguio in the Benguet Mountains of the Philippine Islands, about 170 miles north of Manila, is considered by many as one of the best tropical mountain resorts in the world. It has an elevation of from 4500 to over 5500 feet and surrounded by ranges extending up to almost 8000 feet. It is a region of pines and oaks and has a perpetual temperate climate with occasional frosts. The maximum annual temperature is reported as about 80°F., minimum 53.4°F., with a mean annual temperature of 64.2°F. Open fires are comfortable morning and evening throughout the year and strawberries are grown during eight months of the year. Heavy rains are prevalent however in the summer months. The summer capital of the Archipelago and sanatoria, both civil and military, are located here. Hintze, in his report on the German colony of Espiritu in Brazil says that experience has shown the settlers that it is advisable first to colonize the elevations of from 1000 to 3000 feet, and that if this be done, the later generations can successfully occupy the lowlands, not even excepting the coastal flats. This conclusion is logical but in most tropical places it is next to impossible from economic considerations for people to live away from the steamy coastal plains.

For ill effects of altitude and adaptation to altitude, see p. 1697.

Sunlight.—The solar spectrum contains heat rays extending from infra-red to red, light rays which are yellow, and "chemical rays" extending from the blue to the ultra-violet. The rays reach the earth, according to Langley, in the following percentages:

	Per Cent
Ultra-violet	39
Violet	42
Blue	48
Greenish-blue	54
Yellow	63
Red	70
Infra-red	76

These values are modified considerably by altitude, latitude, season, cloudiness and atmospheric humidity. Only about 50 per cent of the sun's rays reach the surface of the earth at sea-level in contrast to 75 per cent in clear weather at altitudes of 1800 meters. In the clear atmosphere of mountains, there is a higher proportion of light rays and of ultra-violet rays (Bews: 1936).

The spectrum in the tropics extends to the same wave lengths as in the temperate zones. The rays at the violet end of the spectrum which reach the earth are filtered out by the skin itself and by the blood circulating in the capillaries of the skin. These rays can cause hyperemia or burning of the superficial layers of the skin and they promote pigmentation. Ultra-violet rays can kill bacteria. The skin pigment, melanin, absorbs the light rays, except those at the red end of the spectrum. After absorption, the light rays are converted into heat. It is for this reason that Negroes, when exposed to sunlight, sweat more readily than Whites.

Pigmentation of the skin can be promoted not only by direct sunlight but also by reflected or diffused light or by wind. The skin of blonds shows little tendency to become pigmented, with the result that it may burn again and again. Brunettes, as a rule, "tan" readily. When thoroughly pigmented, the skin is highly resistant to sunburn. After excessive exposure of large areas of skin to the sun, white persons whose skins are not protected by pigment, may suffer from severe hyperaemia and blistering of the skin, accompanied by constitutional symptoms such as chills, nausea, headache, vomiting, and a feeling of exhaustion. Local inflammation induced by sunlight has been attributed to the mobilization of histamine from the skin into the tissues and to nutritional alterations of the tissues. Intense sunlight is believed to induce an accumulation of cholesterol in uncovered skin surfaces (Guerrini: 1936).

Sunlight seems to stimulate the nervous system. This effect is beneficial within limits, but repeated exposure to intense sunlight has been thought to be a factor in the causation of "tropical neurasthenia." Not infrequently, intense light whether direct or reflected, causes conjunctivitis, retinitis, photophobia, headache or dizziness.

When overheating of the body results from direct exposure to sunlight in conjunction with high atmospheric temperatures, heat pyrexia (p. 1085) or heat exhaustion (p. 1090) may develop. These effects are not caused, however, by light as such, but by heat.

Among ill effects upon the skin which can be produced by repeated exposure to intense sunlight are *Xeroderma pigmentosum*, severe senile keratosis, and epitheliomatosis. These conditions are seen occasionally in white persons who have lived for a long time in the tropics. Two cases of *Xeroderma pigmentosum* occurring in Spanish-Indian children of the same family have been reported from Yucatan (Shattuck: 1933).

James H. Smith (1931) believed that the distribution and incidence of pellagra are influenced, under certain abnormal conditions, by solar irradiation. He said that an adequate supply of sulphur, as cystine, and a normal metabolism of sulphur, appear to exert a protective influence against the pathologic effects of solar irradiation.

The injurious effect of sunlight upon exposed skin surfaces in typical cases of pellagra has long been known (p. 1058).

Evaluation of Climate

There is a great mass of meteorological data from many parts of the world on atmospheric temperatures, humidity and air movement. The relative frequency of bright sunshine and of cloudiness has been often recorded from many places, also. Solar radiation reaching the earth's surface has been studied quantitatively in certain localities. Something is known too, of the varying proportions of the solar rays of different wave-lengths which reach the earth. But, the physiologist needs far more information about atmospheric and climatic environment than is available today before he can undertake to assess the possible effects upon man of the various components of atmospheric and climatic environment. For example, in addition to the factors already mentioned, dust-content of the atmosphere may be significant by virtue of its power to reduce solar radiation reaching the earth's surface. The possible influence of atmospheric electricity and of cosmic rays is as yet unknown. Some physiologists believe that climate is not accurately reproduced experimentally, even when temperature, humidity, air movement, and dust-content of the air are controlled.

Over a period of many years, attempts have been made to evaluate climatic environment as it affects man. Haldane (1905) emphasized the fact that the readings of the wet bulb thermometer are of greater value than those of the dry bulb for this purpose; and he pointed to the significant effects of humidity and of air movement. Man, however, does not respond like a wet bulb thermometer. The kata-thermometer was designed to overcome some of the recognized difficulties of evaluating atmospheric conditions. Its use was first described by Hill, Angus and Newbold (1928). (See also: Castellani, 1938; p. 44).

Phelps (1928) stated that in American Samoa, persons not exerting themselves are uncomfortable unless the cooling power of the air measured by the wet Kata-thermometer is as great as 11.0, and that comfort in the performance of physical work requires even greater cooling power. Buxton in Samoa found that the readings of the dry Kata-thermometer at 9 a.m. averaged 3.2 for February and 4.3 for July. At noon, the minimum reading of 3.0 was found in December and the maximum 4.6 in July. At 3 p.m. the monthly averages varied from 3.5 to 5.0. Corresponding wet Kata-thermometer readings averaged 13.5 to 18.3, 12.9 to 19.4, and 13.0 to 20.0. These figures, Sundstroem states, do not show any extreme reduction in cooling power but the continuous exposure even to such moderate reductions is an important factor. The amount of cooling power at the disposal of tropical residents is usually diminished by defective housing and unsuitable clothing.

The cooling power of the air may be determined by the wet or dry Kata-thermometer. Orenstein and Ireland (1921) found that when the cooling power of the atmosphere was below six millicalories per square centimeter of body surface per second, and 16 millicalories by the wet Kata thermometer, the working efficiency of a native of the tropics decreases.

Yaglou (1927) recommended for the evaluation of climatic environment the use of "the effective temperature index." It is an arbitrary index of sensation based on the sensation of warmth resulting from various combinations of temperature, humidity and air movement. He said that all measurable physiologic effects of the physical environment upon industrial workers, whether at rest or at work, correlate well with this index. For the sedentary worker, he determined that about 60° effective temperature (E.T.) was optimal, but that it varied with the season of the year. For light work in hot industries, the upper limit of ability to compensate for external temperatures was an E.T. of 90 degrees. The limit for heavier work was an E.T. of 80 degrees.

A similar method of assessing tropical climate has been recommended by Lee and Courtice (1940) for use in classifying tropical climates with reference to problems of settlement by Europeans. The E.T. of Lee and Courtice takes into account environmental temperature, humidity and convection. Some correction can be allowed for radiant energy. Their Figure I, shows a normogram of E.T. by Houghten for men normally clothed and engaged in light work. in which the variables, dry-bulb tempera-

ture, wet-bulb temperature and average air velocity are represented. Given the value of these three variables, the E.T. can be read off directly from the normogram.

Heat Production and Control

The average temperature in the mouth varies from 96°F. to one slightly below 99°F., and the rectal temperature from 97.2°F. between 2 to 5 a.m. to 99.4°F. between 4 to 7 p.m. Pembrey gives the mean daily temperature as being 98.6°F., the maximum 99.5°F. (37.5°C.), and the minimum 96.8°F. (36°C.). It is believed that temperature regulation is the function of a center located in the thalamus. Maintenance of normal body temperature in man depends on the ability to effect a balance between heat production and heat loss. Heat is produced in the body chiefly by the oxidation of foods, particularly carbohydrates and fats. A large proportion of this heat emanates from the muscles, even when they are at rest. Muscular tonus and consequent heat production is increased by nervous tension. Still more heat is produced by shivering and by voluntary muscular activity.

Mechanism of Heat Loss.—Heat is dissipated chiefly from the skin by mechanisms which have been defined by Wiggers (1939) as follows:

Conduction signifies the transfer of energy from one particle to the next through molecular vibration.

Convection signifies the transfer of energy by moving molecules of air which absorb heat and move on.

Radiation signifies the transfer of infra-red (heat) waves through "the ether" without involving a material substance.

Vaporization of water requires the absorption of 0.58 calories for each gram of water vaporized at 37°C.

At an atmospheric temperature approaching that of the human body, vaporization accounts for most of the heat loss from the body. At temperatures above that of the body, the effects of conduction, convection and radiation are reversed. Vaporization then becomes the only significant means of dissipating heat from the body. Vaporization of water takes place chiefly on the surface of the skin and, to a lesser degree, in the lungs. The property of water, in changing from a liquid to a gaseous form, to absorb heat and hold it as latent heat until condensation occurs, makes possible the rapid removal from the body of great quantities of heat when temperature, humidity, air currents, and the clothing worn promote free evaporation.

Hardy and Du Bois (1937) stated that in the temperature range from 30°C. (87°F.) to 32°C. (91°F.) the body eliminates a minimum of heat and that the amount equals the basal heat production. Beyond this range, in temperatures which are either hotter or colder, the heat loss is effective down to 29°C. At temperatures below this level, some mechanism as yet undetermined, induces tension of the muscles or shivering, with resulting increase in basal metabolism and heat production. Du Bois (1938) emphasized the fact that the skin is almost entirely responsible for heat loss and that it is admirably adapted to serve as a heat regulator.

Sweating is the principal means of promoting cooling by vaporization. Experiments have shown (Kuno: 1934) that visible sweating can be produced by thermal agents or by mental or sensory stimuli. The sweating which is caused by thermal agents involves the entire body except the palms of the hands and the soles of the feet. Sweating caused by stimuli other than heat, is usually limited to the palms, the soles and the axillae.

Ordinarily, thermal sweating induced by exposure to moderately high or very high air temperatures begins after a considerable latent period (Kuno: 1934). The amount of sweating is roughly proportional to the degree of heat to which the subject is exposed. In moderate heat, there are marked fluctuations of sweating. At higher temperatures, these fluctuations tend to disappear. It is evident that the cooling effected by sweating is determined not by the quantities of sweat produced but by the amount which evaporates on the surface of the body. Evaporation is affected by various external factors including humidity, air motion and clothing. Nelbach and Harrington in the study of hygroscopic properties of clothing in relation to human heat loss state that in changing a clothed subject from a low to a high relative humidity at the same temperature, the subject appeared to produce more heat than could be accounted for by his metabolic rate. This process is the reverse of evaporation, and was due to the absorption of moisture by the clothing with a resulting evolution of heat. *Science.* (95, 387, 1942.)

The stimulus which induces sweating has been ascribed to increase of body temperature, but Drinker (1936) believes that it is caused, usually, by impulses generated in the nerve endings of the skin.

Invisible, or insensible perspiration is continuous. Benedict and Wardlaw (1932) stated that, within certain limits, this evaporation of water from skin and from the respiratory passages accounts for approximately 25 per cent of the total heat loss from the human body. When measured under basal conditions, the rate of insensible perspiration soon becomes constant. Sleep during the daytime has no significant effect on the rate of invisible perspiration, but it falls markedly during sleep at night. Of the total heat loss by insensible perspiration, about 15 per cent comes from the hands and feet. The rate of loss from the hands and feet is about three times greater than that from the rest of the skin per equal unit of area. In the absence of visible sweating, about 75 per cent of the heat loss is accounted for by conduction, convection and radiation.

Hardy (1934) has pointed out that the skin of the Negro is not truly black and that the visible color of the skin is insignificant so far as its radiating power is concerned. Light of the shorter wave lengths is reflected from the skin, but the longer wave lengths including the infra-red are absorbed. Hardy showed that the skin acts like a "black-body radiator," that its emissivity is close to 100 per cent, and that the presence of water vapor or of CO_2 in the air has no appreciable effect on radiation from the skin.

Physiological Responses to Climatic Heat

Basal metabolism may fall moderately within a few days after entering the hot tropics. This reduction may persist until the individual returns to a cool climate, after which the metabolism returns rapidly to the original level. (Drinker: 1936). When heat causes a rise of body temperature, the metabolism increases in consequence. Such increases of temperature commonly follow physical exertion in a hot environment.

Mason's (1940) long series of observations on 21 English and American women who went to live in southern India, reveals the fact that the metabolic response of individuals differs. One group (Type I), comprising 13 of the women (62 per cent), showed a fall of metabolic rate averaging about 10 per cent; whereas the remaining 8 women (Type II), showed no significant change in the metabolic rate. Mason says in conclusion: "There is as yet no real evidence that one type of tropical response is a better adaptation than the other."

MacGregor and Loh (1941) have also shown that basal metabolism may show a definite reaction to tropical environment in certain individuals and be absent in others.

Body Temperature.—According to Drinker (1936), a slight increase of body temperature is the rule in the tropics. In Mason's cases of Type I (those showing a decrease in basal metabolism), the average body temperature remained unchanged; but the temperature for those of Type II (no significant reduction of basal metabolism), showed an average increase of 0.6°F.

Castellani (1938) said that he and Chalmers had not found any change in body temperature in passages going to and from the tropics or during residence therein "provided that the individuals observed were normal." Neither did he observe any difference of body temperature between well nourished, healthy natives and Europeans, "with due allowance for individual and seasonal differences and the effects of exercise and clothing." He discussed matters relating to body temperature in considerable detail.

Pulse Rate.—Drinker (1936) said that a slight decrease in pulse rate usually occurs but that changes reported are "very insignificant." Manson's Type I, showed an average fall in pulse rate of 11.8 whereas, in Type II, the fall was only 7.2 beats per minute. The changes in pulse rate in different individuals ranged from an increase of one beat to a fall of twenty-one beats per minute.

In the majority of Europeans, no change in the pulse rate was observed by Castellani (1938) either on entering the Tropics or after residing there. In a few persons the rate showed a slight increase at first. This disappeared "after acclimatization."

Systolic Blood Pressure.—Drinker recognized the existence, as a rule of a very slight decrease. Reporting on 18 female subjects, Mason observed an average decrease of 5 mm. in the systolic and in the diastolic pressures as well. The range of variation

in the systolic pressure was from plus 9 mm. to minus 22 mm. The range for the diastolic pressure was from plus 2 mm. to minus 25 mm. Other observations inclined Mason to believe that "circulatory changes as reflected in pulse rate and blood pressure may not take place so quickly as changes in heat production or body temperature. . . ."

Roddis and Cooper (Castellani: 1938), who observed a large number of naval officers while on duty in West Indian waters, found the average systolic blood pressure to be 11.5 points lower than the standard for the temperate zone. The blood pressure fell gradually. Sixteen of the officers showed an average rise of systolic pressure of 9 points, one month after return to the temperate zone.

Respiration.—The evaporation of water from the lungs assists in the regulation of body temperature. Due to the increased distribution of blood to the surface of the body, the lungs weigh less in a hot than in a cold or temperate climate. The capacity of the lungs is therefore increased.

Drinker (1936) said that the respiration rate tends to decrease and the minute volume to increase. The greater minute volume promotes cooling by increased evaporation of water.

Blood Volume.—Plasma volume was studied in four subjects by Talbott, Edwards, Dill and Drastich (1933) in Boston and subsequently in the same subjects at Boulder City, Nevada, where the summer temperatures are higher than those of the hot, moist tropics where the humidity is low. They reported that the small differences observed were within the limits of error of the method. However, Barcroft and associates (Drinker: 1936) on an expedition from England to Peru, found that blood volume increased as the tropics were entered. Commenting on these observations, Drinker said that the necessary increase of sweating must require a constantly higher blood supply to the skin and, if the blood volume did not increase, impoverishment of the internal organs would result. It seems possible that such an impoverishment may occur in some of the individuals who fail to adapt adequately to tropical environments and who, in consequence, exhibit marked decrease of efficiency when living in a tropical environment.

In a very recent article, Forbes, Dill and Hall (1940) reported their observations on 10 whites who had moved to a hot, damp climate. Small increases of about 5 per cent in the volume of the blood and in the plasma volume were observed.

Interstitial Fluid.—The authors quoted above, observed in the same series of subjects a decrease in interstitial fluid (outside the cells and outside the blood vessels) which averaged 11 per cent. The range, however, varied from minus 34 per cent to plus 26 per cent.

Composition of the Blood.—Red cells are apt to be increased and white cells decreased slightly. Blood sugar may be low. A slight alkalosis has been reported, particularly in persons of sedentary habit, but it disappears with the assumption of periodic exercise (Drinker; 1936).

Sundstroem (1926) has reported observations on the blood of white residents of northern Australia. Some of his findings are at variance with those of other observers. He recorded reduced levels for total phosphorous in the blood. Talbott et al (1933) reported that changes from normal in the constituents of the blood are small after adaptation to climatic heat has occurred.

Commenting on the pallor of the skin of the face, which is common in white residents of the tropics, Castellani (1938) said that there is no foundation for the belief that this pallor is caused by a "physiological anemia." In his experience, blood sugar is not decreased.

Digestive Functions.—It is common, in periods of hot weather in a temperate climate, to experience a marked loss of appetite. After living for some time in the Tropics, northern Whites are apt to exhibit a persistent reduction of appetite which is often accompanied by an increased craving for highly spiced foods and for liquor before the evening meal. The loss of appetite might well be attributed to a depression of the digestive functions and a reduction of the digestive secretions. Castellani (1938) has pointed out that Arnold's experiments on dogs, which were kept in an artificially warm and moist atmosphere, showed a decrease in gastric secretion and a fall in acidity. He

Melaniferous Leucocytes.—These are usually large mononuclears bearing particles of pigment; macrophages which have ingested malarial pigment and are characteristic of malaria and blackwater fever.

Melioidosis.—The disease may be considered as a very virulent type of glanders and, in those cases which do not die in the first 2 or 3 days, the pustules and subcutaneous abscesses may suggest either ordinary glanders or pustular syphilides. Involvement of bone takes place if the patient lives beyond the second or third week. Fulminant types suggest plague or cholera and die in 2 or 3 days. Later, there may be lung involvement, which suggests miliary tuberculosis or typhoid fever. Abscesses of liver and kidney may further complicate the diagnosis. Diagnosis is difficult unless the organism is cultivated from blood, urine or faeces. The blood serum usually shows an agglutination for *Bacterium whitmani*. Death occurs almost invariably.

Menorrhagia and Metrorrhagia.—Either of these conditions may occur when women first arrive in the tropics. Their exact relationship to change of climate is not known. Should metrorrhagia persist and produce constitutional symptoms or the anaemia become grave the woman should terminate her residence in the tropics. Before these conditions may be said to be due to the change of climate all other causes, such as, endometritis, subinvolution, displacement of the uterus, lacerations, tumors, ovarian disease and alcohol should be excluded. After the age of 35 malignancy should be excluded in all cases.

Mononucleosis Acute.—See p. 1650.

Mouth, Diagnostic Signs Obtained from.—In considering sore mouth one should also keep in mind the diagnostic odors of the breath such as in alcoholism and uraemia. Common causes of sore mouth are stomatitis, syphilis, pyorrhea, tonsillitis and thrush. The onset of pernicious anaemia may be accompanied by a fairly characteristic red, raw tongue and gums.

Herpes Labialis is not so common in tropical malarias as in those of temperate climates. It is absent in plague pneumonia.

Leishmaniasis.—In kala-azar and possibly in malaria we may have gangrenous conditions of the cheek, as cancrum oris.

Leprosy.—In leprosy the nodules which form on the inside of the cheeks and fauces tend to show ulceration and thickenings. The discharges from the ulcerations in the nose, especially those on the vomer, reach the pharynx and such leprosy bacilli-containing discharges may be expectorated and cause one to consider the material as coming from the lungs.

Onyalai.—A very peculiar disease of Portuguese West Africa and also the Soudan region, known as onyalai is characterized by the appearance of blood-distended vesicles of the mucosa of the cheeks and hard palate. The tongue is often swollen. The skin may show haemorrhages and haematuria is not infrequent. The mouth blebs vary in size from that of a split pea to a diameter of ½ inch or more. The cause is unknown. In severe cases there is anaemia and a marked decrease in the blood platelets. The blood may show a normal coagulation time but there is usually a prolongation of the bleeding time. The onset is sudden and the mortality high.

Pellagra.—In pellagra there is moist fissuring at the angles of the mouth with a large indented tongue with central coating and bare tip and sides. There is often a glairy mucus covering these red borders on the side. The fungiform papillae are prominent. Later on the tongue may become fissured and uniformly red. The buccal mucosa shows a carmine flush. The gums are tender but there is not the tendency to aphthous ulcers one sees in sprue. The flow of saliva is frequently increased.

Sprue.—In sprue there is at first great sensitiveness of the buccal mucosa so that articles of moderate pungency give rise to painful burning sensations. The tongue becomes quite sore with vesicle formation along borders and tip which soon turn into ulcers. Ulcerations may also occur on the buccal mucosa, particularly at the site of the posterior upper and lower molar teeth (Crombie's ulcer).

The congestion causes a great increase in mucus especially about the faucial pillars and pharynx. Ulcers are common about the fraenum of the tongue. While the tongue is coated at first, with red ulcerated tip and sides it later becomes bare of any coating, red and finally even glazed as though varnished. It is at times fissured.

Leukaemias.—Gradual painless enlargement of the spleen to an enormous size is characteristic of myeloid leukaemia, lymphatic leukaemia, pseudo-leukaemia infantum.

Malaria.—Splenic enlargement and tenderness are important points in diagnosis of malaria. In acute malignant tertian infections the spleen is often diffluent so that it is liable to rupture upon slight injury. The palpation of the spleen in acute malaria is a difficult procedure. Although it may be considerably enlarged, it is so soft that palpation is difficult. One should even exercise care not to palpate the spleen too violently and the possibility of accident should be thought of in making a spleen puncture. The typical malaria spleen is the ague cake of malarial cachexia. Here we have a greatly enlarged spleen with a thickened capsule and firm consistence. This spleen may fill up one side of the abdomen.

Malta Fever.—The splenic enlargement in this disease usually corresponds about to that of typhoid fever. At times, however, the size may be so great as even to suggest kala-azar.

Relapsing Fever.—Splenic enlargement and tenderness are marked features in this disease, often being noted early in the course.

Rickets.—The spleen may be readily palpable in rickets. The malnutrition, rachitic rosary, presence of Harrison's groove, projection of sternum, painful joints, craniotabes, enlarged abdomen, profuse sweating and tendency to atony is present. Blood chemistry shows reduction of inorganic phosphates.

Rocky Mountain Fever.—One point of distinction between spotted fever of the Rocky Mountains and typhus fever may be that the spleen of the former disease is usually enlarged three or four times the normal, while that of typhus fever shows no increase in size. The palpable spleen of Rocky Mountain fever is firm instead of soft as with typhus fever.

Schistosomiasis.—The spleen may be enlarged in Japanese schistosomiasis as well as in African schistosomiasis due to either *S. haematobium* or *S. mansoni.*

Splenic Anaemia.—(Banti's disease.) Enlarged spleen, leucopenia, recurring hematemesis and secondary anaemia. Must be differentiated from syphilis with anaemia accompanied by splenomegaly.

Syphilis.—In congenital syphilis the spleen is often enlarged along with the liver. In syphilitic cirrhosis of the liver the spleen may be greatly enlarged. Syphilis may be the cause of the same clinical and blood picture as found in Banti's disease. Syphilis may produce an anaemia associated with splenomegaly and every such case having a positive Kahn serum reaction should be regarded as luetic until proven otherwise.

Sprue.—This interesting disease may be diagnosed by: (1) Diarrhoea with the characteristic white stools, which may be intimately mixed with bubbles of gas giving them a frothy appearance. (2) Tongue and mouth lesions in which the tongue is denuded of epithelium and shows inflammatory changes. (3) Loss of weight. (4) Anaemia may be moderate to severe. The red blood count may fall to 1,000,000 per c.mm., and resemble the picture of pernicious anaemia. (5) Small liver. (6) The neutral fat and fatty acid ratio in sprue may become 1–5 against a normal of neutral fat 1, fatty acid 2. Sprue may simulate pernicious anaemia, pellagra, malignancy of the pancreas, syphilis, and dysentery. In malignancy of the pancreas the neutral fat and fatty acid ratio helps differentiate as in this condition the neutral fat in the stool may be as high as 15, to fatty acids 1. Pernicious anaemia, syphilis and dysentery may be differentiated by thorough laboratory study and the absence of true sprue stool differentiates pellagra. Sprue is now recognized as a nutritional deficiency disease. See p. 1023. See diarrhoea for etiology of tetany in fatty or chylous diarrhoea.

Stomach and Oesophagus.—Very important in diagnosis is a tenderness in the pyloric end of the stomach, which is brought out by attempting to palpate the epigastric region. It is often marked in yellow fever and acute pernicious beriberi as well as in blackwater fever and bilious remittent fever. We also frequently have epigastric tenderness, extending to the right, in ancylostomiasis. Hookworm patients are often "pot-bellied" and the craving for eating unusual articles, as earth, may be connected with the gastric hyperacidity which the patient desires to neutralize with alkaline earth.

Pellagra gives eructations and pyrosis and very common is a burning sensation extending from the stomach along the line of the oesophagus.

lost when men are working stripped to the waist may be absorbed by a close fitting elastic cotton union suit and distributed uniformly over the entire surface by capillary action. This eliminates the burning effect upon areas of the body which otherwise become dry, while other parts of the body surface are adequately cooled by the evaporation of abundant perspiration.

Eijkman found no perceptible difference in the number of sweat glands between the brown and the white race, but counts made by Clark show that the darker skins contain a larger percentage of sweat glands than the lighter. Persons who do not perspire or who have a defective sudorific system are not suited for residence in the tropics.

The sweat secretion of the white man in the tropics goes beyond the limits of efficient heat regulation and become superfluous so that the skin and clothes become moist. This together with the warm moist air increases the frequency, especially in the recent arrival, of common bacterial and mycotic skin infections, and lichen tropicus or so-called prickly heat, from which last-named condition, the native seems to be exempt.

Hair and Nails.—It has been stated that the hair and nails grow more rapidly in the tropics than in the temperate zone. Sundstroem (1926) however, found that the hair grew at a rate which averaged 11% slower in the tropics than in a temperate climate. The most rapid rate coincided with the first part of the oppressive season when other functions were also improved, while a sudden decline in the rate of growth occurred when the metabolic processes showed signs of slowing down. A considerable stimulation of growth followed a return to a cooler climate which then continued in cycles according to the season. A maximum growth was then noted in June and a minimum in December. The total nail growth was also retarded 11% in the tropics and the seasonal variations were in general identical with those observed for the growth of the hair.

Acclimatization of the Individual

The foregoing pages dealing with Heat Production and Heat Control and with Physiological Responses to Climatic Heat, indicate that little is known with certainty about acclimatization.

Lee (1935) has emphasized the complexity of the problem of physiological adaptation to climatic heat. He believes that: "Failure of adaptation may be thermal, circulatory, ionic or anhydraemic," and that in certain cases, several of these kinds of failure may operate together.

In a manuscript unpublished at this writing, Dill (1941) said: "A survey of the contributions of Huntington, Petersen, Mills, and Price, in the field of medical climatology reveals a lack of agreement in some areas and evidences of overemphasis on the effects of climate on man."

There is no longer any doubt that excessive heat throws an increased burden upon the heart. Failure of the circulatory mechanism to respond to the increased stress incidental to exposure to heat is the principal cause of heat exhaustion (p. 1090).

Asmussen (1940) said that acclimatization to humid heat involves regulation of the circulation in such a way that it can be kept at a practically normal level when at rest or during work. He assumed that the slight increase of blood volume and the slightly higher pulse rate (observed by Forbes, Dill and Hall: 1940) were the main factors of this adaptation. He said further, that circulatory failure during work develops more readily in humid heat because of the difficulties of heat dissipation; and that the larger amount of blood demanded for circulation through the skin tends to decrease the cardiac output.

It has been proved that northern Whites, during continued exposure to heat, soon develop a marked increase in the secretion of sweat and that the percentage of sodium chloride eliminated in the sweat becomes greatly reduced (p. 1091).

Alterations of body temperature, basal metabolism and pulse rate, which have been observed in certain individuals, do not occur in other individuals.

Age.—The age groups which suffer most frequently from the effects of climatic heat are the very young and the elderly. Apparently, the power of infants to regulate body temperature is comparatively low. This factor, perhaps, operates also in the elderly but the principal cause of their susceptibility to heat is the decreased power of the circulatory apparatus which is incidental to age (Shattuck and Hilferty: 1933).

Drinker (1936) considered it safe to say that the effects of tropical residence are more pronounced in the children of northern Whites than they are in adults. In accordance with this view, it has long been customary for the English living in India to send their children of school age to England. However, many white Americans living in the Canal Zone of Panama have not sent their children away. An eminent physician living there, has told me that such children seem to do well, provided that hygienic requirements are observed.

Sex.—Women of northern races usually suffer more than do men, from the effects of a period of residence in the tropics. Although physiological differences may play a part, it is highly probable that comparative idleness and lack of exercise are of greater importance.

Race.—Robinson, Dill, et al (1941) compared the responses to physical work of White and of Negro share-croppers in the State of Mississippi during the hot weather. Then the results showed that the capacity of the Whites for work under these circumstances was inferior to that of the Negro. This fact is in accord with the general belief that races originating in the tropics are better adapted to life there than are northern Whites.

The Negroes lost less weight during work and showed a smaller rise in body temperature and less increase of heart-rate than the Whites. Moreover, the haemoglobin of the Negroes was about nine-tenths and the leucocyte count was about half that of the Whites. The respiratory rate of the Negroes was more rapid than that of Whites. The acid-base balance of arterial blood showed no dependence on race.

For many years, statistical information has shown a high incidence of heat effects among natives of the British Isles residing in India or in other hot countries. On the other hand, the Dutch in Java, and the North Americans in the Philippine Islands and in the American tropics, suffer far less frequently from heat effects, even though they take little precaution against exposure to hot sunlight. Although the French fear the sun nearly as much as the English, they have suffered little from heat effects in their colonies in recent years (Shattuck and Hilferty: 1936).

Environment.—In the broad sense, acclimatization requires not only physiological adaptation to climate but also hygienic and psychic adaptation to the environment. Not enough is known as yet about these matters to enable one to determine in advance whether or not an individual from a temperate climate is likely to do well or ill in the tropics. A few indications may be mentioned, however.

Persons who have an abnormally high basal metabolic rate should avoid the Tropics. Those who do not sweat easily may fail to respond with the increase of sweating which is needed for the dissipation of heat. Habitual nervous instability and lack of poise indicate that adaptation to life in a tropical environment may be difficult. To make the necessary hygienic and psychic adaptations, requires strong character, determination and knowledge.

Environmental influences other than climate, which may seriously impair the efficiency of white persons from the temperate zones who have become residents of the tropics, may be listed as follows:

(1) Comparative social isolation and consequent paucity of intellectual stimuli.
(2) Monotony of work.
(3) Dearth of wholesome recreation.
(4) Unhygienic living.
(5) Depressing effects of disease.

Influences numbered 1, 2 and 3, have been discussed under Reactions of the Nervous System and number 4 has been dealt with in the section on Personal Hygiene.

Acclimatization of the Soldier.—Singer (1940) has described concisely certain tests which he believes to be significant for determining the adaptability or adaptation of soldiers to climatic changes; and also the methods used for increasing the power to adapt to pronounced changes of weather or of climate.

Acclimatization to Altitude.—Most of the symptoms which are experienced by persons who ascend rapidly to altitudes of 10,000 feet or more, have been attributed by recent students of the subject to diminished partial pressure of oxygen and the conse-

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PERSONAL HYGIENE

Foreword.—Information about the prevention and control of specific diseases can be found in the sections devoted to these diseases and in books dealing primarily with preventive medicine and public health. Little information is obtainable from these books, however, regarding personal hygiene and prophylaxis for the individual. This subject, therefore, will be dealt with in the ensuing pages.

Preliminary Precautions

Medical Examination.—Before making an extended visit to the Tropics it is advisable to have a medical examination to determine physical fitness. The presence of any serious circulatory disorder renders a visit to the tropics inadvisable. Persons so afflicted should scrupulously avoid high altitudes whether on land or in the air. Other contraindications to be borne in mind are hyperthyroidism, deficient sweating on exposure to heat, and disorders of digestion. Nervous or emotional instability is likely to be aggravated to a serious degree by prolonged residence in the tropics.

Dental Examination.—Because good dentists are scarce in the tropics, the teeth should be most carefully examined and treated, if necessary, before leaving home. Fillings of doubtful durability should be replaced.

Vaccination against smallpox and against typhoid fever, including paratyphoid A and B, is advisable unless such vaccinations have been performed within two years or the individual is believed to be immune.

Anti-typhus (p. 951) and anti-yellow fever inoculations (p. 1674) have been advised for those who are likely to be exposed to these diseases. Because some reports show that vaccination against cholera (p. 633) usually becomes ineffective after a year or even some months, it is well to have it performed by the local health services, if and when an epidemic is encountered.

Plague vaccine (p. 701) confers a considerable degree of active immunity which may last for a year or more. The protection conferred by passive immunization by means of an anti-plague serum is of short duration. Local health services can usually be relied on to perform either of these inoculations wherever plague prevails.

Equipment of special character which is important for health, should be carefully selected and obtained before going to the Tropics. As a means of protection against malaria, for example, a mosquito net of suitable design and quality (p. 1744) should be packed in a piece of luggage which will always be available. Boots or leggings for protecting the ankles from the bites of mosquitoes should be included (see p. 1713).

One or two canteens should be carried by persons who expect to travel much in the Tropics (see Water: p. 1728).

A warm woollen overcoat is indispensable in parts of the Tropics where the nights may be cold or where the temperature may fall rapidly. Light woollen clothing, a woollen bathrobe and a sweater are valuable to prevent chilling, even where fluctuations of temperature are not extreme. This is so because exposure to heat renders one hypersensitive to moderate fluctuations of temperature. Cotton clothing and headgear suitable for ordinary wear in the Tropics can usually be purchased there more cheaply than in the United States.

Food

Food in the tropics, except in the best hotels, is apt to be unappetizing or unwholesome. Meats are, usually, very tough. Soups and various other foods are often excessively greasy. Raw salads and fruits which are not pealed at the table must usually be regarded as unsafe to eat, and fruit of any kind may be scarce. Continuing heat seems to depress the digestive functions and it tends to promote diarrhoea or constipation. In order to promote good digestion, one should avoid excessive fatigue, eat slowly, chew thoroughly, ingest an adequate amount of fluid, and take physical exercise regularly.

Diet.—The quantity and kind of food eaten by tropical races differs widely. Many individuals among them are undernourished. It does not seem possible in the present state of knowledge to base advice to northern Whites upon any secure foundation. Theoretical considerations suggest that the proportion of the heat producing foods which are ordinarily ingested; i.e. carbohydrate and fats, might advantageously be reduced when in a hot climate, and that meats could be taken freely. It is by no means clear that the total caloric intake should be decreased for any considerable length of time, because the increase of body temperature, which commonly occurs after exercise in hot weather, increases metabolism. Obese persons can well afford to lose some weight, but others should endeavor to maintain body weight, approximately, at the usual level. A diet of reduced caloric value may be adequate for sedentary workers. Persons who exercise much require abundant food.

Whatever the diet in other respects, it is essential that the accessory food factors, such as iron and other mineral salts, and the vitamins (p. 1030), should be ingested in abundance. Fruits are important, not only for their vitamin content but also because they promote normal action of the bowels. If taken in excess, they may cause diarrhoea. Highly spiced foods may soon help to combat loss of appetite.

Milk and Cream.—In parts of the tropics no fresh milk is obtainable. The milk of cows, goats, buffaloes and even of sheep may be used for drinking but reasonably clean milk is rarely available. Fresh milk or cream should, therefore, be boiled before use, or, at least efficiently pasteurized. Pasteurization at 145°F. to 150°F. for 30 minutes does not kill all the bacteria, but can be relied upon to destroy most of those that are pathogenic. After pasteurizing, the milk should be cooled quickly to prevent the rapid growth of surviving bacteria.

The accessory food factors in milk, except vitamin C, are not much affected by pasteurization. Precautions required for buttermilk or skimmed milk and milk to be made into ice-cream are the same as for whole milk.

Various brands of dried, powdered milk are believed to be excellent substitutes for fresh milk. The powdered milk should be dissolved in boiling water in a clean container and used soon thereafter. Unless to be used in quantity, the dried milk should be packed in small tins. Otherwise, it is important to protect the unused portion from moisture and from insects by keeping it in a container which has a tight cover.

Powdered milk, with suitable modification, can be recommended for infant feeding. It has approximately the same food values as pasteurized milk. Because it contains little vitamin C (p. 1074), this vitamin must be provided from some other source.

Butter made from unclean milk is a possible cause of tuberculosis or of other infectious diseases. Butter is prepared, however, from pasteurized cream under sanitary conditions in some parts of the tropics, as elsewhere. When the cleanliness of locally prepared butter is in doubt, canned butter or oleomargarine may be used. Canned butter of reliable brands probably contains most if not all of the vitamin A and provitamin originally present. If fortified by the addition of vitamin D, this vitamin also should be retained. (Nutritive Aspects of Canned Foods: 1937; p. 36; and personal letter.)

Oleomargarines are of two types; namely, those which are made chiefly from vegetable oils or fats and those which are derived from animal products. Most of the animal oleomargarines are devoid of vitamin A. To some brands, however, concentrates of vitamins A and D are added. Those which have been accepted by the Council no

Foods and Nutrition of the American Medical Association provide not less than 7500 U.S.P. units of vitamin A per pound, an amount which approximates the vitamin A content of an equal amount of good butter. Owing to a ruling of the Bureau of Animal Industry of the United States Department of Agriculture, oleomargarines produced from animal fats may not be fortified with vitamin A. Therefore, in the United States only oleomargarines made from vegetable fats can be so fortified. (Accepted Foods and their Nutritional Significance: 1939; p. 40; and personal letter.)

Cheese.—There is a great difference in cheeses with regard to their potentialities for carrying pathogenic organisms. The well ripened hard cheeses which have been stored for from 6 months to 2 years are less likely to be dangerous than are those of the soft curd type. The latter are to be avoided wherever sanitation is primitive.

Frozen desserts, such as ice-cream and "water ices" are potentially dangerous unless prepared from pasteurized milk or from pure water and clean fruit juices. The safest rule is to avoid frozen desserts except in places where the sanitary code is highly developed and well enforced. The subject has been dealt with in detail by the United States Public Health Service (1940).

Vegetables which have been thoroughly boiled lose some of their vitamins. Nevertheless, because vegetables are likely to have been contaminated, they should not be eaten raw in the Tropics. This rule applies particularly to salads made from raw, fresh vegetables, to "greens" used for garnishing, to celery, and the like. It has not been shown that such vegetables can be rendered safe by washing them in a weak solution of permanganate of potash. Tomatoes can be dipped into boiling water. The skin quickly becomes loose and can then be peeled off easily. It is well to make the fullest use of fresh native vegetables rather than to eat canned vegetables.

Fruits.—Fresh native fruits should be eaten freely. Fruits growing near to the ground should be treated as vegetables. Those growing higher, should be peeled. It is safer to peel the fruit at the table than to have it done in a kitchen where it may not be handled in a cleanly manner. Similarly, fresh fruit juices or coconut milk may become contaminated if carelessly handled in the kitchen.

Infant Feeding.—Breast fed infants do well as a rule in the tropics and while there is no doubt that both mother and child benefit thereby, each case must necessarily be judged on its merits and an analysis made of the mother's milk if the child does not thrive. Harston states that the quality of the milk of European mothers compares very favorably with that of human milk in temperate climates and quotes in support a table giving the results of analyses made in Manila, of the milk of American women. These analyses, confirmed by Harston's observations, show that the proportion of proteid is less in nursing mothers in the tropics, but that the percentage of fat is much higher. On the other hand, the results obtained by Jacob in Panama are not in agreement with those in Manila. He found that the milk of American women tended to deteriorate in quality as the infant's age increases and that the milk of colored women is richer. White women should nurse their children for at least two months, but where this is impossible a wet nurse or artificial feeding must be employed. The greatest care must be taken in the selection of a wet nurse. Both the nurse and her child must be examined for signs and symptoms of disease and this examination fortified by such laboratory tests as may be thought necessary, including, however, a blood test in every case.

Artificial Feeding.—Balfour states, "of course, if good and pure cow's milk can be obtained from sanitary dairies, then it should be used diluted and sweetened in the usual way. It is, however, comparatively rarely available, and, even when it is forthcoming, samples should be carefully analysed, for it frequently differs from the milk of cows in temperate climates. It is usually more concentrated and the percentage of total solids and of fat is higher. Failing cow's milk, goat's milk, which is often procurable, may be tried and has much to commend it, notably because its casein forms a flocculent curd and not hard cheesy masses. Hence it is more easily digested than cow's milk. The cream is in finer globules than is the fat of cow's milk and thus it is not so much in evidence, but the quantity is ample. The goat is practically immune to tuberculosis, is a cleanly animal, and, if properly fed and looked after, will not eat garbage or soiled

fodder, and its milk under these conditions is quite palatable and can be 'humanized, and used with advantage." All raw milk should of course be pasteurized.

Buffalo or caribou milk is unsuitable owing to its very high fat content.

Deeks in Panama obtained excellent results in infant feeding by using a milk composed of one part condensed milk to two or three parts of evaporated milk when diluted with seven to eight or more parts of water. In the Philippines a mixture of unsweetened sterilized milk and cream has likewise given good results. Canned milks however must be treated as fresh cow's milk and be properly refrigerated and protected from vermin when the cans are opened. As fresh cans are required daily these methods have the disadvantage of being expensive.

Dried milks are now employed to an increasing extent in the tropics. They are prepared either by the rapid drying of fresh milk on rollers heated by water or steam, after which the milk solids are powdered with or without the admixture of lactose, or by the projection of milk in the form of a very fine spray into a closed room where the water is removed by currents of hot clean dry air causing the milk solids to fall to the floor in the form of a fine dry powder.

All dried milk intended for infants' food in the tropics must be packed in hermetically sealed tins. If packed in this way the dried preparation will keep quite as well as condensed milk. Blackham states that during the war some of the stocks of dried milk were on hand a long time and that in the Himalayas, in 1917, there were tins of dried milk which must have been imported in 1915 or earlier. The results obtained gave evidence of the excellent keeping qualities of the brand of dried milk used.

A large number of samples of dried milk have been examined at the Lister Institute of Preventive Medicine, with the result that in no case could the tubercle bacillus be found. As the result of a series of experiments by Blackham no spore-bearing organisms were found. Although the samples were not actually sterile, only organisms such as the hay bacillus were found, and pathogenic or sewage organisms were always absent. Dried milk has the additional advantage that ice is not required. Each feeding is constructed with boiled sterile water, sugar or such modification as is deemed necessary immediately before it is to be used. The only obligatory precautions to be observed are to keep the powdered milk dry and free from insects in the original container by means of the tightly fitting cover. Anti-scorbutics such as orange or lemon juice are indicated and water must be given in amounts sufficient to replace the water lost from the skin to avoid constipation and irritation of the kidneys by a concentrated urine.

Beverages

Water.—Safe municipal water is not obtainable in many communities in the tropics. Except in the smallest places, or in the interior, bottled water of a reliable brand is usually available. Water which has been bottled on the premises is likely to be unsafe for drinking. The safest plan is to boil the drinking water yourself each day. For this purpose, a large enamel-ware kettle or a pot with a cover is useful. Preferably, the pot should have a lip for pouring. Otherwise, a ladle with hooked handle can be used. The ladle should be kept hanging in the pot while the water is being boiled. After use, it should be returned to the pot without having been allowed to touch anything.

When travelling, it is important always to carry plenty of drinking water in canteens or other containers. They can be filled with boiled water, or the water in them can be chlorinated by the addition of a substance such as halazone. Theoretically, one tablet of halazone is sufficient to chlorinate one quart (or about 1000 cc.) of water. But, if the water contains organic matter, two tablets or even more may be required. After putting in the chlorinating substance, the canteen should be shaken to promote solution of the tablet. One half hour later, the canteen should be shaken again. Then, if enough of the chlorinating substance has been used, the odor of free chlorine can be detected by its smell, on removal of the stopper. If there is no odor of chlorine, more of the chlorinating substance should be put in and the procedure repeated. Adequate chlorination can be relied upon to kill bacteria of the typhoid and dysentery group and the vegetative forms of *E. histolytica* as well though some believe that the vegatative forms

can not live in water. Probably it does not render amoebic cysts non-viable. Therefore, boiled water is to be preferred.

Drinking water should not be filtered after boiling or put into earthen vessels for cooling because filters and earthern vessels are difficult to keep clean. Filter pumps have serious disadvantages for use in the field. Fresh coconut milk is at times an excellent substitute for water. Beer is less satisfactory for slaking thirst.

When sweating is profuse, the body may be in need of sodium chloride as well as water. Under these conditions, it is advisable to add about 10 grains (0.6 Gm.) of table salt to each pint (about 500 cc.) of drinking water.

Ice is little safer than the water from which it was made. Unless known to be clean, it should not be allowed to come into direct contact with beverages or with food which is ready to serve.

Alcoholic beverages should be taken in great moderation, if at all. An excellent rule is not to drink liquor in hot weather until after sundown. Neglect of this rule may invite serious effects from heat. For the sake of the digestion, strong liquor should be well diluted before being consumed. Neither water nor ice of doubtful purity can safely be put into it. A cold drink is refreshing, but iced drinks taken in hot weather sometimes cause indigestion. Beer is satisfying to some individuals but tends to increase thirst in others.

Most observers agree that an increase of appetite and a stimulation of the digestive function frequently appears soon after arrival in the tropics. This is often followed, even within a short time, by a lessened desire for food, especially animal food and a greater demand for spiced articles of diet. The latter are represented by the curries of India and the chilli of Mexico.

Manson-Bahr has emphasized the special dangers in the tropics of over indulgence in food and drink beyond safe physiological limits and the tendency to the production of "tropical liver" (see p. 534).

Regimen

Habits of Life.—In general, habits of life have racial or national characteristics and depend, among civilized people, almost entirely upon tradition irrespective of environment, though tradition in its early stages arises from a lengthy adaptation to special circumstances. Therefore, while the habits of the natives of a country are generally more or less well adapted to the conditions of the climate, and to the stage of civilization at which the race has arrived, the habits of the white races are adapted to the temperate regions from which they come and necessarily must be adjusted to the new conditions. Habits make environment unless environment is permitted to regulate habits; consequently the circumstances and conditions induced by persistence in habits unsuited to the climate are among the chief and outstanding causes of the discomforts and dangers of tropical residence. Moreover, there is the feeling among new arrivals, which is only corrected by experience, that the precautions taken or the habits of life observed by the older residents are trivial, unjustified, or absurd. Climatic adaptation is essential and must be assisted by correct habits and the acceptance of environmental circumstances which are in conformity with the existing conditions of climate and temperature.

Exercise.—A certain amount of systematic daily exercise in the open air, adjusted to the age and physical condition of the individual, is essential for the maintenance of good health in the tropics. It promotes sleep and rest, stimulates peristalsis thereby assisting the body to expel effete matter and overcome any tendency to constipation. The concomitant perspiration leads to greater excretion of organic matter by the sweat glands, and the more rapid respiration, to more thorough aeration of the blood. Exercise properly taken improves the appetite and capacity for work and materially lessens irritability of the central nervous system. New arrivals stimulated by the change of environment frequently have a tendency to indulge in exercise until they are unduly fatigued with the result that they overtax their strength and experience exhaustion of the vital forces rather than beneficial effects. Desirable forms of exercise such as walking, swimming, riding, tennis, golf, and boating should be taken in the early morning or late afternoon, must not be overdone, and should be rotated to prevent

monotony. It is a mistake to play tennis in the hot sun or to seek a rapid coat of tan by an unduly prolonged exposure to the sun's rays. Care must be taken to avoid chill after exercise. When possible a warm bath should be taken immediately followed by a cool shower and a vigorous rub-down and a change of clothes, otherwise protection from chilling may be afforded by a sweater or other suitable garment.

Work and Rest.—Cilento (1925) stated that experiments in New Guinea, both with white men and with natives, demonstrated that the quality and quantity of work done between the hours of 6 a.m. and 2 p.m. considerably exceeded in both respects that done during any other set of hours, no matter where chosen. In most tropical countries work ceases between the hours of 11 a.m. or 12 Noon and 2 or 3 p.m. the usual interval of two hours being devoted to lunch and rest. The daily work period, from 7 a.m.–5 p.m. with two hours rest from 11 a.m. to 1 p.m., was observed during the construction of the Panama Canal apparently without deleterious effects upon the workers, who for the most part were engaged in hard physical labor. According to Cilento this routine is well-intentioned but faultily conceived, the rest period serving to accentuate the feeling of lassitude on the part of the workers. Production and contentment will undoubtedly be increased if the work is finished at 2 p.m. so that the worker may indulge in rest or exercise or both during the remainder of the day.

Most people need at least eight hours of unbroken sleep at night in the tropics. Some prefer to sleep on a veranda protected from mosquitoes by a thorough screening or by a bed net. Sundstroem, from observations in Townsville, found that the bed net reduced the already poor cooling power by one-third. At the time of the experiment, the bed without the net would have offered a tolerable cooling power for a resting person. After drawing the net this was impossible. In a few experiments, when comparing a bed on the veranda with one indoors, it was found that the bed with drawn net on the veranda offered the same cooling power as the bed without net indoors. And yet people continue to sleep indoors. If work begins early, late hours should be avoided, for as Balfour states, they tend to produce insomnia and the latter often heralds a breakdown. The mid-day siesta is commonly observed by most tropical peoples but the more energetic Anglo-Saxon may dispense with it entirely. It is very necessary for white women, if they are to preserve their looks and vitality, and for white children.

Bathing.—Frequent daily bathing for obvious reasons is both desirable and necessary in the tropics. Tepid or warm baths are to be preferred both because of better cleansing properties and to avoid chills. In the case of those who have had malaria and in whom the disease has not been entirely eradicated, a relapse is likely to follow a cold bath. Strong healthy people often derive benefit from a cool shower after a warm bath as it removes the feeling of lassitude sometimes induced by a warm bath. Cold bathing is not recommended for infants, children, debilitated or old people. Balfour states that shaving the axillae, a native custom in many parts of the tropics, would not only tend towards comfort but prevent the risk of contracting those fungus diseases so common in the tropics.

Dental Hygiene.—Putrefactive and fermentative processes are more common and active in the tropics and infections of the alveolar mucous membrane frequently occur in persons who do not give sufficient care to the teeth. Accumulations of tartar on the teeth irritate the gums and frequently lead to serious dental infections which timely removal would have effectually prevented. As caries progresses rapidly, all cavities should receive immediate and appropriate dental treatment. It has been said that a clean tooth never decays. The teeth should be thoroughly and properly cleansed twice a day with a tooth brush of only moderate hardness and brushed along the axis of the tooth from the gum margin toward the free surface and not crosswise, as the latter causes an irritation of the gums and may eventually cause them to recede thus exposing the roots. Material lodged in the interstices between the teeth should be removed by the aid of dental floss. The teeth are part of a skeletal system that is susceptible to nutritional influences. Kappes from an examination of school children found that the only feature which seems to be of definite etiologic significance in preventing decay is a diet composed largely of fruits and vegetables and concluded that heredity, infectious diseases, and the care of the teeth appear to be of little, if any, significance.

Recreation is essential for the maintenance of mental and emotional normality. Sports games, intellectual pursuits and hobbies should, therefore, be encouraged.

To escape from one's emotions is not possible. Carthew stated that the most important thing is to learn how to judge the emotions, how to value them, how to control them, how to divert them into harmless, or, better still, into useful channels; and this is what should be taught to the prospective wanderer before he ventures into the tropics. Sublimation or canalization is the process by which instinctive emotions are diverted from their original ends and redirected to purposes satisfying to the individual and of value to the community.

Neurasthema.—Mental irritability and nervous breakdown in the tropics, which in the absence of demonstrable organic lesions are commonly regarded as due to climate, are frequently included in the term "tropical neurasthenia" for lack of a better term.

Crumpston has called most of the neurasthenia of North Australia "kitchen neurasthenia," Plehn has referred to outbursts of passion as "tropical frenzy," and Sir Havelock Charles has described similar neurasthenic manifestations characterized by shortness of temper, forgetfulness, sleeplessness, and disinclination to work under the title "Punjab head."

The real cause of these nervous manifestations can undoubtedly be traced in most instances to faulty habits of life such as overfeeding, poor elimination, lack of exercise, faulty daily routine, excesses, the absence of any creative interest, work, or hobby unhygienic surroundings, endocrine disturbances, and the depression of previous or concomitant parasitic infections. All physical agents such as heat, light, humidity, winds, and glare are merely aggravating factors and not the primary cause, which is essentially psychological in character.

Wyborn states that a person removed from his native surroundings to which his mentality is adjusted, to a new environment, whether tropical or polar, will suffer until new and mentally satisfactory associations and mental adjustments have been made. Depending upon the mental development of the individual even from infancy, this change may or may not occur.

A tendency to forget names and an inability to recall immediately familiar trifling details at will, a common defect among tropical residents, is directly related to lack of exercise and disappears when adequate exercise is taken. Hintze points out that although all women can live in the tropics if they live rationally, those who are poor and so are forced to work hard, do uncommonly better than those for whom everything is done.

Types of Tropical Neurasthenia.—Apart from that due to definite organic cause, neurasthenia as observed in the tropics is of two types. The one type is due to indolence and self-indulgence, and the other to the depressing monotony of hard work under unfavorable circumstances. Cilento states that an instability of the mental equilibrium is manifested by fits of exuberance alternating with states of depression. Unwarranted irritability over trivial matters is a leading early symptom and even blasts of fury are not uncommon especially with male patients. A lack of self-confidence is often a prominent underlying cause and is associated with a diminution of mental ability, activity, and the power of concentration. An unresponsive memory added to these disabilities greatly diminishes the working capacity. The realization of this mental state by the patients and their futile attempts at readjustment produce even greater lack of self-confidence and an aggravation of the entire syndrome. As noted by Cook in old residents of Uganda, nervous irritability is shown by a response to small stimuli, increased reflexes, tachycardia, and insomnia. Dreams of a depressing or a terrifying nature are frequent symptoms which upon analysis show most definitely some complex based on the non-creative monotony of the life of the individual, some apparently great failure to adapt themselves to the circumstances of life as they are.

White persons in the tropics and natives following the daily routine of trivial clerkships, together with the neurasthenics of temperate climates, are all alike, victims to that craving for self-expression that their vocations deny them. They are fixed in circumstances to which they cannot adapt themselves mentally, and their eccentric actions are evidence of their revolt. The ostentation and invalidism that attracts

comment or invites pity, or makes the patients at least a centre of passing interest are attributed to an irresistible mental demand for recognition. To this also must be attributed the excessive and uncontrolled outbursts of passion they suffer when, by the thwarting of some whim or the contradiction of some expressed opinion, the inferiority complex under which they labor is called suddenly to the border of consciousness. Second only to the will to personal survival, and closely related to it, is the desire to create, and whether this is effected by actual procreation or by the consummation of some work that holds the dominant interest of its possessor, or by both, it alone can satisfy the universal and imperative demand for self-fulfilment.

If such a demand is persistently foiled up to the point at which denial seems final, the mental tension increases to and beyond the maximum of mental resiliency, and the breaking strain is represented by over reaction to stimuli, by intervals of alternating despondency and excitement, and, finally, by that irresponsibility, eccentricity, and lack of concentration known as neurasthenia. At that stage, whether the patient resides at the equator or at the poles, or anywhere intermediate, unless something sufficiently strong attaches the interest, neurasthenia must inevitably supervene.

Unnatural Life for Women.—If the life of the ordinary woman in the tropics, where there are subject native races, is examined, it is obvious that her creative interest, in a very considerable proportion of cases, will find no expression whatever in any of the three ways which are most common; namely, in her children, in her home, or in her outside interests. Many women coming to the tropics refuse to have children, having been persuaded it is a dangerous and, maybe, a fatal proceeding. Those that do have them, often leave them to the care of a native nurse almost exclusively. Frequently they are persuaded that they are unable to nurse the child, and cease to stand in an intimate parental relationship, as would result from the care and nourishment of their own child. Many bereave themselves of their children at their most engaging age, by sending them out of the country.

In many places it is considered undignified for the white woman to attend personally to any of the duties of the household, and these are left entirely in the charge of house boys, of whose native tongue she is probably almost entirely ignorant.

As outside interests are few and trivial, the one outstanding characteristic of tropical society becomes its lack of communal interests and this very lack produces a state of mutual misunderstanding which tends to embitter the few social relationships which are possible. The great deficiencies are lack of interest and lack of physical exercise. If a family is not dependent for peace of mind upon outside social influences and finds contentment in its own family life, there is no reason to believe that mental or nervous conditions will develop among the members even during the comparative isolation in periods of excessive rainfall. With unmarried persons the problem is more difficult.

Prophylactic Measures

Exposure to Sun.—The requisites for protection from the sun will be discussed under Clothing (p. 1710) and Headgear (p. 1712). Megaw (1939), who was thoroughly familiar with conditions in India, where the sun is greatly feared, has well said that the sun's rays in the tropics have no mysterious properties and that the serious harm which may result from them is an effect of heat (see Acute Effects of Heat: p. 1082).

Exposure to Cold.—Chilling is to be avoided, especially by those who have had malaria and who may not be entirely free from the disease. Megaw (1939), however, believes that the healthy body should be able to accomodate itself to moderate changes of temperature and that maintenance of full vigor requires exposure to such changes. Hence the debility which commonly develops in persons who are exposed for long periods to an equable climate characterized by high temperature and humidity.

The methods of prophylaxis against important diseases are described in the sections devoted to these diseases or in that on sanitation. A few other matters which may not have been covered are mentioned below.

Food Poisoning.—Putrefactive changes take place more readily in all foods, especially sea foods, and toxin producing bacteria grow more rapidly in foods such as meats,

fish, milk, and even canned foods, so there is more danger of febrile disturbances and gastrointestinal derangements due to spoilage in the tropics than in the temperate regions. Then, too, the handling of foods without protective coverings, by natives favors the dissemination of the food poisoning group of microorganisms. Food poisoning when it follows the ingestion of decomposed tissue is not due to decomposition products resulting from spoilage, but to the toxin capable of causing disease in man often caused by some member of the *Salmonella enteritidis* (*B. enteritidis*) or paratyphoid group of microorganisms with which the food has been contaminated.

It is possible for foods, especially meats, fish, and shell fish, to be contaminated with microorganisms of the food poisoning group without undergoing decomposition. The opportunities for contamination with the putrefactive bacteria are so great, however, that these foods usually undergo decomposition promptly unless great care is used to protect them and keep them well refrigerated. The chances that contamination will occur are much greater in warm weather, when exposed to dust, and where such foods are not handled with scrupulous cleanliness.

The only safe rule is to observe great care in the stowage, handling, and preparation of food and to avoid eating any food that shows evidence of spoilage. It may not cause symptoms if eaten, but decomposition is evidence of contamination and it may also be contaminated with bacteria that do yield toxic products (see Chap. XVI). Some fish are intrinsically poisonous at all times and others are poisonous only at certain times of the year. While the judgment of natives is not infallible, it is a fairly safe procedure to follow in the identification of safe edible sea food.

Care of the Eyes.—Glare is well known as a cause of headache and this is probably caused partly by damage to the retina and partly by overstimulation of the visual cortex. Gibbs states that the ill effects of light upon the eyes is due not so much to the ultraviolet rays as to the glare of the reflected light. The direct rays of the sun are very disagreeable and injurious in all latitudes but, as they are instinctively avoided, seldom strike the retina. The glare in the lowlands of the Philippine Islands is due not so much to the light reflected from the surface of the earth, which is usually more or less covered with vegetation, and which reflects the longer waves of the spectrum to a greater extent than the shorter, as to the reflections from the sky. A clear blue sky so frequent in the mountains during a considerable portion of the year is seldom disagreeable to the eyes even though the intensity of the sunlight is greater than in lower altitudes. These differences in the effects of light may be accounted for by the greater proportion of cirrus clouds, haze, and dust-laden atmosphere of the lower altitudes.

MacCallan pointed out that while fatigue, ill-health, and worry bring out latent defects in the eyes in any country, a hot climate causes greater fatigue than a temperate one, and this fatigue may lead to fatigue-indigestion with resulting physical depression. Trifling errors of refraction, or slight degrees of heterophoria, exerted effects quite out of proportion to their actual severity. In a highly sensitive patient, whose nerves were constantly being jarred by physical or mental discomforts, the correction of a very small degree of astigmatism might make all the difference between happiness and misery. The healthy emmetropic eye of the European becomes painfully effected by the sun's glare. It is the heat rays from the red end of the spectrum which cause this. To prevent the effects of glare, MacCallan advises the wearing of protective goggles of Crookes B or B2 material. There are, he states, other varieties of protective glasses, which theoretically are more absorbent of the heat rays than Crookes glasses, such as peacock blue, green, and amber, but in his own experience of a large number of cases he found that ordinary glass in which was included, if necessary, a very small ametropic correction, was all that was required. Sun, dust, and wind, may also cause pinguecula and pterygium. In dusty seasons it is most advisable to wash the dust from the eyelids which collects there and which may contain septic material. This should be done three times a day. In many cases he found this simple precaution sufficient to prevent constantly recurring attacks of conjunctivitis.

It is probable that a lens with a slight amber or other tint, will alleviate the glare produced by the intense tropical light, reduce the tendency to headache, may be worn both within and out of doors, and will be more comfortable than a lens of

plain or untinted glass. Deeply tinted glasses, however, are not necessary in most instances.

Phelps has said that blindness caused by corneal ulcers resulting from untreated acute infectious conjunctivitis in Samoa has been practically stopped by distributing a 5% solution of argyrol to the mayors of the villages and instructing them how to use it. This disease was caused by any one of a number of common microorganisms and by a Gram-positive diplococcus. The spread was due to ignorance, flies, and filthy habits.

Woodruff points out the nuisance of the glare from houses painted white in the tropics and mentions the better colors of green, dark yellow, and brown. The gradual disappearance of the white buildings in the business part of Colombo, and the appearance of new buildings colored brown indicates the correctness of his views (Castellani).

Sunburn.—The rays of greater refrangibility in the violet and ultra-violet portions of the spectrum cause the phenomenon of sunburn with its resultant irritation of the nerve-endings and hyperaemia of the peripheral tissues, but as these rays have very little power of penetration, the skin can in time amply protect itself by pigmentation. As is well known the white skin will become sunburned whether in a strong blast of air or not and even by diffuse or reflected rays. That the direct rays are not necessary is evidenced by sunburn acquired on bright cloudy days, or while in the shade but exposed to rays reflected from a bright surface.

Sunburn may vary from a simple hyperaemia of the peripheral tissues to burns of the second degree or possibly with sufficiently long exposure to one of the third degree. A patient following exhaustion while swimming fell asleep on a white sand beach near Colon, Panama, and exposed his unprotected back to the direct rays of the sun from about 2 to 4 p.m. This exposure was followed by massive bleb formation over his entire back with some destruction of tissue.

Protection from chemical rays is easily accomplished and has been obtained as long as man has worn clothes. A white cotton shirt and white trousers are sufficient protection against these rays. Phalen observes that the effects of the chemical rays are probably exhausted upon the skin alone. Even in the deeper layers of the skin, there is a constantly circulating layer of blood which is probably much more efficient as a protection against the chemical rays than is a permanent layer of pigment. If the effect upon the skin can be accepted as a measure of actinic influence, then khaki of itself is sufficiently protective. Many men have their arms protected by a single layer of khaki and, after years of service in the tropics, have no more pigment in the skin thereof than upon arrival.

It is an error for a person to expose large areas of the body to direct rays of the sun in the tropics, as is often practiced in the temperate zone for the purpose of producing tanning or pigmentation of the skin. Excessive or prolonged exposure by persons with fair complexion and very little pigment in their skin has been followed by constitutional symptoms such as chills, nausea, vomiting, and exhaustion. Whether more serious or lasting effects may follow such exposure is not known at present.

When sun-burn does occur a simple lotion may be prepared by dissolving a level tablespoonful of powdered boric acid and 20 drops of carbolic acid to one-half pint of hot water. The solution should not be rubbed into the skin but daubed on the inflamed surface every half hour if necessary with a small piece of cotton or sprayed on with an atomizer. If no medical supplies are available, cold compresses will give relief to badly burned areas.

Laundering.—Supervision of laundry work receives too little attention in the tropics. Modern laundries ordinarily do not exist so that the washing is done by natives according to their own custom. This custom, which is destructive to fabrics and buttons, consists in placing clothes on stones along any dirty stream or collection of water which happens to be convenient and beating them with wooden paddles. When, as frequently occurs, native communities use stagnant pools or tanks for washing purposes, the danger of contracting a parasitic skin disease is greatly increased. As an instance of this, an officer contracted both scabies and ringworm from underclothes washed in this manner. All underwear was sterilized except one suit which was overlooked. Both diseases reappeared when this suit was worn again four months later. In the Orient nearly all

communicable skin diseases are popularly called "dhobie" or washerman's itch. Private individuals or families should, if possible, insist upon the attendance of the washerman instead of allowing him to take clothing away.

Clothing

Types of Clothing.—When selecting clothing, it is important to bear in mind that free ventilation of the skin is essential to promote cooling by evaporation of perspiration, and that dissipation of heat from the skin takes place more rapidly from uncovered parts of the body.

In a hot, equable climate, all garments should be loose, thin, and light in weight. The shirt should be worn open at the neck and the sleeves should be short. Instead of trousers, Megaw (1939) advises cotton "shorts" which are buttoned to the shirt to render the use of a belt unnecessary. Shorts are not suitable when protection is needed from insects or from leeches, or in areas where abrasions of legs may occur.

When a coat must be worn, suspenders may be more comfortable than a belt. Longitudinal slits under the arms of shirt and coat promote ventilation and are visible only when the arms are raised. Cotton suits for use in the hotter parts of the tropics should be made of very light material. Even so, a heavily starched suit is impervious to air. It has been suggested that those who do not perspire properly, need wear no underclothing. However, underclothing is preferable. It should be of light and porous material which will absorb the perspiration and permit it to evaporate gradually.

The type of clothing to be worn by either sex may require modifications for protection from insect bites. Other modifications are required wherever sudden or considerable changes of temperature occur. Under these conditions, a sleeveless sweater or a light overcoat should be at hand. Lightly woven woollen is preferable for outer clothing where the diurnal range of temperature is considerable.

After prolonged exposure to constant heat, the body becomes extremely sensitive to changes of temperature. A drop of more than 10°F. produces a disagreeable sensation of cold and unless warmer clothing is put on promptly, a further drop may cause chilling and an attack of diarrhoea.

Spine pads are useless. "Cholera belts" have the disadvantage that they may become soaked with perspiration and thus increase the chances of chilling the abdomen. They tend, also, to induce prickly heat.

Color.—White will generally absorb the smallest amount of radiated energy but Wood has shown that ultra-violet light is not reflected from all white surfaces, as those treated with zinc oxide or Chinese white appear black when photographed by this light. The following table compiled by Rubner gives the absorptive powers of different colored clothing materials compared with white as 1.00:

White.......	1.00	Dark green.	1.61
Light yellow	1.02	Red........	1.68
Light green.	1.40	Light brown	1.98
Dark yellow.	1.40	Black.......	2.08

It will be noted that black can absorb over twice as much heat as white. Experiments with rabbits by Gibbs have demonstrated the superiority of the protective value of white over the darker colors. White, gray and black rabbits were exposed at the same time to the sun in Manila under identical conditions. The black rabbits died in thirty-three minutes, the gray in one hour and thirty-two minutes, while the white rabbits recovered after the same exposure to the sun accorded the gray.

Fabrics of various colors and weaves were exposed to the mid-day sun by Grabham at Khartoum in 1918 on bright still days, with thermometers inserted so that the bulbs were covered by a single thickness and separated from the support by at least five layers of the same cloth. The following temperatures, the mean of three experiments, were recorded:

	°C.		°C.
Black, thin lining.....	85.0	Khaki, "solaro"..........	72.9
Black, cotton serge...	83.9	Khaki, wool cord..........	72.8
Black, woolen serge...	83.0	Khaki, thin...............	72.3
Blue, dark, cotton....	79.2	Blue, pale, old cotton......	72.2
Khaki, heavy, washed	76.0	White duck, linen.........	61.9
Khaki, heavy, new...	75.7	White drill, washed cotton.	59.5
Khaki, wool serge....	75.1	White drill, new...........	57.6
Surrounding air......	45		

Thus white is the coolest color and light blue, a color commonly used in garments of the Chinese coolies and Egyptian laborers, compares favorably with khaki. While temperatures in the sun depend upon the color exposed, they are also influenced by surface texture and the rate at which heat is lost by convection. The differences in temperature noted with the various kinds of khaki were thought to be due to differences of color as some of the test pieces were of a distinctly lighter color than others. The "Solaro" and similar fabrics, which were used extensively at the time the "actinic ray" theory was regarded as of paramount importance, do not appear to afford protection superior to that of thin khaki. Practically no difference in the temperature was observed when layers of white cloth were placed under khaki.

An extensive experiment in the daily use of orange red underwear by 500 men which was conducted in the Philippines was reported by Phalen in 1910. An equal number of men wearing white underwear were observed at the same time as controls. His conclusions were that the slightly heavier orange red underwear added materially to the burden of heat upon the system, which is undoubtedly the great cause of tropical deterioration. "To balance this it is protective against the chemical ray, the influence of which is regarded as of little moment, and which is sufficiently excluded by khaki clothing and the campaign hat worn at present. Certainly no beneficial effect whatever was observed from the use of this clothing. This experiment suggests that any efforts toward increasing the physical well-being and efficiency of the soldier shall be directed toward protecting him from the debilitating effects of heat and humidity."

Materials.—Articles of clothing hold moisture either in the form of droplets between the fibers or by absorption of the water by the fibers. Animal fibers absorb more water than do plant fibers. Wet fibers swell and thus tend to occlude the interstitial spaces. On the other hand, water held in the interstices occlude these spaces even more. Cotton fabrics have a greater tendency than woolen to stick to the body when wet. This is a disadvantage because it occludes the air space which should exist between the clothing and the body. Wool, especially when loosely woven, appears to be the only fabric which still permits, when saturated, the passage of air between the fibers. The interposed layer of air prevents too rapid evaporation of water from woolen underwear, and chilling of the body by rapid evaporation from woolen outer garments. The hygroscopic power of wool tends to keep undergarments of other materials dry as evidenced by the practice among soldiers of wearing woolen over cotton socks during long marches in hot weather. Woolen materials, however, are less cleanly than cotton, silk, or linen. They show the outward signs of dirt less but tend to shrink on washing, and often irritate the skin when worn next to it. With the exception of the woolen overshirt and socks for active work in the open, and light merino underwear for children and debilitated persons during the cooler months, white or light colored, cotton, linen, or silk will be found more comfortable in the tropics. Linen is more durable, weight for weight, than cotton and because of the smoothness of its fibers, soils less readily. It is also said to be cooler and more absorbent than cotton.

The best interests of hygiene in the tropics are served by clothing that can not only be readily and repeatedly washed, but that can also be sterilized or disinfected by boil-

ing. Parasitic skin diseases are very prevalent in the tropics and it is regarded as next to impossible to cure those caused by moulds or mites without thorough and repeated disinfection of all clothing in contact with the infected skin.

Cotton is comparatively cheap, fairly durable, may be obtained in any color or weight, and is perhaps the best available material for both underwear and outer garments. The experiments in the Philippines would seem to indicate that ultra-violet rays are largely stopped by the garments exposed to the sun and that white cotton underwear will amply protect the skin from such rays as may possibly filter through. As clothes tend to become more easily soiled through increased perspiration, many more changes are required than in temperate climates. White is the color of choice, but where the nature of the work precludes this color, the lack of laundry facilities, or the cost of washing would be prohibitive, khaki or similar material may be substituted.

Silks, such as taffetas, mercerized cotton, leather, and rubber materials do not keep well in the tropics. White cotton and linen articles such as sheets and table cloths, when stored outside of a dry room, tend to become spotted with moulds, and rust stains due to a fungus It has been shown that many of the air borne fungi are either killed or inhibited in their growth by a liberal application of formaldehyde. Consequently, sprinkling formaldehyde on bedding and table linen or the interposition of paraformaldehyde tablets incased in small gauze sacks will prevent or reduce to a large extent the development of these moulds, troublesome from the viewpoint of the housekeeper.

Headgear.—An excellent substitute for an umbrella or the crude and cumbersome hats of native workmanship is a helmet with a large brim which will shade the neck. The protection accorded by the pith helmet depends upon its light color, the low conductivity of the pith crown, and the provision made for free ventilation. The heavy helmets frequently seen in the tropics cause fatigue of the head and neck. The cork helmet withstands rain but it is heavier and less cool than the pith helmet. The maximum of comfort and protection will be provided by a helmet which is white in color, light in weight, and constructed to allow free circulation of air. Ventilation is obtained by openings at the top of the head piece and an air space formed by the insertion of cork disks between the head band and the inner walls of the helmet. Protection for the pith helmet against rain may be secured by a removable waterproof cover. Corson found that with a maximum shade temperature of 86° to 88°F. and a fairly strong breeze, the felt hat and the red fez showed temperatures within the hats of from 105° to 112°F. with exposures of from 10 minutes to half an hour or longer, ladies' felt hats 108°F., white pith helmets 97° to 98°F. Panama straw hats rarely showed temperatures above 100°F. After wearing a Panama hat for a year in tropical Africa, he preferred it to the heavier "Wolseley" helmet which he had worn previously.

I have known adults who could go bare-headed and unharmed in Indo-China, in the Belgian Congo and in the Amazon basin. One of them was almost completely bald.

In Panama, very little care is taken to protect the head and neck against the sun. At the white schools in Balboa and other towns on the Isthmus the hat is said to be the exception rather than the rule. This practice is observed largely by children and young adults and apparently is increasing during the summer in the United States. Acting upon the belief that the sun has no power to produce damage by direct exposure and that the ill-effects resulting from strong sunlight are due to the action of the glare upon the eyes, many walk about in the sun with the eyes protected by dark glasses or dark eye-shades, but unprovided with hats, and apparently suffer no ill-effects.

Certain individuals, and among them most of those who have experienced heat pyrexia, are extremely sensitive to hot sunlight which falls upon the head or upon the neck. They may, nevertheless, obtain adequate protection in the tropics by wearing a good helmet.

Leggings.—For riding, for walking in the bush, or to protect the ankles from insects, the canvas legging is comfortable and reasonably adequate. The spiral, woollen puttee has many disadvantages and the leather puttee is needlessly heavy. If the legging is to be used for riding, the lacing should lead through the eyelets instead of being held in place by hooks which catch on the stirrup.

To protect the ankles from mosquitoes in the evening, close-fitting, white leggings are desirable both for men or women. Men can wear them under a pair of white trousers. The lower end of the legging should lap over the white shoes like a spat, leaving no opportunity for mosquitoes to bite the feet.

Boots, Shoes and Socks.—Low white canvas shoes are perhaps the most comfortable foot wear for the tropics with white buckskin next. Outside of settled communities, however, high shoes with leggings or puttees, or boots, are essential. The best results are obtained by fitting boots or shoes over a thick pair of socks to allow for the swelling of the feet, which is associated with hot weather, and for their expansion during long walks or exercise. Comfort is increased by foot wear, not too tight over the instep, with plenty of room for the toes, and with pliable soles. The tendency of the skin to maceration and the prevalence of skin infections require that particular attention be accorded the care of the feet. It is desirable, therefore, to use new footwear for short distances before wearing them for any length of time. New boots may be made more pliable by a liberal application of neat's foot oil or castor oil. Insects are not attracted by white clothing, consequently the wearing of white socks or stockings renders the wearer less liable to bites on the lower extremities.

The long "mosquito boot," made of thin, white canvas or of light soft leather, is very comfortable for evening wear. It protects the ankles completely from mosquitoes.

Women's Clothing.—Fashion sets the style and cut of the clothes in all localities. Sundstroem pointed out that the white woman as well as the white man wastes in unnecessary clothing a large reserve cooling power. With proper clothing, this cooling power, when added to that constantly available, would greatly improve the heat elimination even to the point at which many of the secondary and probably harmful tropical effects would disappear. As for men, loose fitting garments of white or light colored washable material are indicated for women in the tropics. Light weight cotton and linen materials are said to be cooler than silk. Well constructed white parasols, preferably lined with green, will be found most agreeable to both the eyes and the uncovered skin when exposed to the sun during the hottest part of the day.

Children's Clothing.—Care must be taken to provide timely and proper changes of clothing as children are very susceptible to variations in temperature. In general, loose fitting garments allowing free circulation of air, and made of material both absorbent and porous, are necessary. Infants require, the year round, underwear of silk or mixtures of silk or cotton and wool varying only in thickness to suit the season. Long clothes are generally condemned by all authorities. Waterproof fabrics may be used to protect children's mattresses, but, as they cause irritation of the skin, must never be placed over an infant's napkin. One piece play suits of khaki or light blue with loosely woven nainsook combination underwear to prevent constriction at the waist and irritation of the skin are ideal during the hot weather. Most authorities, however, believe that underwear of light flannel which in addition to being warm is both absorbent and porous is preferable during the cooler weather and throughout the rainy season. A nightgown of thin flannel with a running tape at the bottom for infants and one piece pajamas or knitted sleeping suits such as the Arnold's for older children will prevent exposure of the skin at night with its attendant danger of chill. To prevent hookworm, shoes must be worn in all countries where the disease is endemic. Sandals have been recommended, but it is doubtful if they protect the feet as well as shoes.

Rain Clothes.—Tropical conditions require that waterproof clothing be made with seams cemented and stitched, as rubber cement tends to soften in the heat. While all rain clothes are hot, the poncho or waterproof cape affords better ventilation and is probably the most comfortable. Ordinary fabrics may be waterproofed by immersion in a solution of five ounces of lanolin or wool fat dissolved in a gallon of petrol. The excess of the solution is then removed and the articles dried in a current of air. Garments treated by this process, which is described by Lukis and Blackham, are said to protect well from the rain and yet are permeable to the air and can withstand moderate washing. Lack of ventilation causes the garment to become wet inside as a result of condensation.

The Tropical Habitation

Housing.—The primitive house, as exemplified by many native huts, is essentially a one roomed enclosure provided with a roof. Larger houses are collections of such primitive rooms arranged more or less in accordance with custom, comfort and convenience. In the tropics, the objects to be attained in building construction are to allow the maximum amount of shade and of ventilation or air circulation, and to exclude the greatest amount of heat. The kind of house to be built will depend upon the architectural customs or styles and upon the environmental conditions.

There are two general types, one of which may be called the bungalow pattern and the other the Spanish type of house. The first type is characterized by wide verandas, broad passages, the largest possible amount of window space, and the elevation of the structure two to three feet above the ground on wooden or preferably concrete posts to permit free circulation of air beneath the house. The rooms are arranged in a single row, one room in depth so far as possible to facilitate the free passage of the breeze.

Elevation of the structure on posts, either wood, creosoted wood, concrete, brick, or stone, is a very great advantage and if sufficiently high will provide utilizable space beneath the house. White paint or even white wash applied to the under surface of the flooring, even though the space is not utilized, is an advantage, as it tends to prevent the harboring of mosquitoes which prefer dark windless shelters. All posts should be equipped with a gutter for oil or other suitable preparation to repel ants.

The second type is of massive construction without verandas but with thick walls and built about a central court or "patio." High narrow shuttered windows are provided which are kept closed during the day to exclude both heat and light. Coolness of the outside walls, which in the old Spanish house was obtained through thickness, may also be provided for by double concrete walls, properly rat-proofed, containing an air space. Modern, hollow, building tiles should be very effective in this type of house. The "Spanish type" seems best adapted to hot inland towns while the "bungalow type" is more favored and perhaps better adapted for humid coastal areas.

Damp-proof courses of slate, glazed or well tarred brick, sheet lead, tile, or other impermeable material must be inserted horizontally through the entire thickness to prevent moisture from rising in the walls.

Location.—From the standpoint of health, the primary considerations in the site for a dwelling are its location with reference to prevailing winds, mosquito and fly producing areas, and native populations. The opportunities for a good water and food supply and the proper disposal of excreta and refuse of course require consideration.

The situation should have a cheerful outlook and be elevated, preferably on a slope with good natural drainage. Sandy or gravelly soil bears weight well and is said to be the best. Clay tends to shrink or swell with changes in the weather and to cause cracks in buildings placed upon it. Soil with a constant level of ground water is preferable to that in which the subsoil water varies with the season. The ground water should be 6 to 8 feet below the surface. A site to windward of swamp and native communities will reduce the number of mosquitoes. Anopheline mosquitoes instinctively fly toward a light and are capable of flights over a distance of 2 miles or more. A stretch of open water 1 mile in width does not oppose an effective barrier. During the construction of the Panama Canal it was the practice to remove vegetation and keep the grass closely cut for a radius of 200 yards about white settlements to prevent mosquitoes finding shelter during the day. While this is not ordinarily practicable, it is well to keep grass near a dwelling cut and avoid masses of vegetation in landscape gardening. Vines about a veranda reduce ventilation and afford resting places for mosquitoes. The house should be so placed as to obtain the greatest advantage from the prevailing winds. Balfour recommends that the building be oriented to face north and south.

Roofs may be either peaked or flat, but the flat roof is somewhat hotter than the former. In either case coolness can be enhanced by a double roof with an interspace connected with the outer air to provide ventilation. Thorough screening of all openings is necessary to prevent the entrance of bats and rats. Galvanized iron roofs are very hot during the day but lose heat rapidly at night. When this material is used, the rooms

should be protected by a ceiling and the intervening air space well ventilated. A thatched roof has the advantage of coolness but it harbors insects and other pests.

In many tropical countries the verandas, in addition to providing shade and protecting the house proper from sun and rain, are used as living rooms as they are open to the breeze.

To promote comfort, verandas should be much larger and more extensive in proportion to the house than in temperate climates. A veranda should be built not only to provide shade but to act as a shaft to assist in the circulation of air. Frequently they are too enclosed to serve this purpose and hot air, banks against the side of the house in a deep layer which warms the adjacent rooms. To avoid the accumulation of hot air, verandas should be double roofed and the interspace should be well ventilated.

Materials.—Aside from the native thatch or bamboo, buildings may be constructed of mud, wood, sun-dried brick, burnt brick, stone and concrete. Grabham conducted experiments in 1915 with building bricks. A hole was drilled from the end so that the bulb of an inserted thermometer was about the center of the brick. A pair of burnt bricks and a pair of sun-dried bricks were used. One of each pair was white-washed while the other was left plain. They were then exposed to the sun for two consecutive days. The readings of the thermometers at 2 p.m. were as follows:

Material	February 9 2 p.m.	February 10 2 p.m.
Plain burnt brick	57.8°C.	53.3°C.
Plain sun-dried brick	54.3	50.4
Mud brick, whitewashed	49.5	46.9
Burnt brick, whitewashed	48.3	46.3
Official maximum	33.4	31.1

He concluded that the texture probably contributed to the difference in favor of the sun-dried brick.

In Panama very satisfactory types of one and two story dwellings were built of wood during the early days of canal construction. They conformed in general to the "bungalow" pattern and had wide verandas on three and in some instances on four sides which were equipped with either single or double screened doors. These doors always opened outward to prevent the ingress of mosquitoes and other insects when they were opened. Chamberlain states that it is particularly important that windows should be either of the French swinging type, or else slide into the wall in order to permit complete opening of the window apertures. The method of screening in the Canal Zone is to screen the entire porch and not the windows or doors of the house proper. This allows much more air to circulate than would pass through screened windows and doors. He did not find the houses hot or stuffy as a result of the screening.

Houses built of concrete have great advantage over wood, in that they are permanent, cannot be harmed by white ants (termites), are less likely to become infested with ordinary ants and cockroaches, and are more easily rat-proofed.

In some recently constructed buildings on the Canal Zone, Chamberlain found that it was entirely practicable to make all the concrete members very small and, by thus almost eliminating the walls, very free ventilation was secured. Sufficient overhang on each story was provided to keep out the rains which occur on the Isthmus, and which are seldom accompanied by wind. In countries subject to driving rains, it would be necessary either to build very wide overhangs, or else to provide sashes which could be closed when necessary.

Color.—Grabham conducted experiments at Wady Halfa in 1921 with flasks painted with colors in common use. White and black standards were provided. The white flask was treated with a lime wash which gave a white mat surface and the black standard flask was coated with a mixture of lamp-black and varnish which dried with a dull black surface. The results of the experiments are shown in the following table:

	Number of observations	Temperatures in degrees, 12:30 p.m. C.	F.	Excess above whitewash, deg F.
Black standard		66.2	151.2	36.3
Black paint (9)		66.8	152.2	35.2
Brown paint (8) dark		63.2	145.8	29.9
Green paint (4) dark		63.8	146.8	30 9
Gray paint (7)		61.0	141.8	25.9
Cement wash (P. W. D.)	14	61	142.7	26.8
Khaki paint (6)	8	59	138.4	22.5
Red paint (P. W. D.)	13	58	136.8	20.9
Aluminum paint	22	58	136.6	20.7
Dull red paint (P. W. D.)	14	57	135.9	20.0
Plain tin	22	57.2	135.0	19.1
Scarlet paint (10)		56.3	133.3	17.4
Straw paint (5)		54.2	129.6	13.7
Cream paint (2)		53.0	127.4	11.5
Cream enamel (1)		53.0	127.4	11.5
White enamel (3)	7	50.2	122.4	6.5
White enamel (P. W. D.)	14	49.6	121.3	5.4
White standard		46.6	115.9	

As a practical test, one-half of the corrugated galvanized iron roof of a barge was white washed, while the other half remaining in the usual condition presented the rather dull surface of weathered metal. In the sunshine of the middle hours of the day the difference in the temperatures of the two halves of the roof was very striking. The plain metal became very hot while the whitewashed part remained cool and could be handled with comfort. In moving about under the roof which was low, the radiant heat from the plain half was oppressive while beneath the whitewashed part it was possible to remain in comfort without a hat. He is of the opinion that a roof painted white is as efficient as an unpainted roof lined with wood. The glare from the white roof, however, would necessarily have to be taken into consideration.

Objection has been raised against the color of cement on account of its effect upon the eyes. Cement is not a pure white and soon weathers to an even darker color. Chamberlain is of the opinion that the only objection to concrete is the monotony of the color which causes a depressing effect. This could be easily overcome if tiles were embedded to a certain extent in the exterior of buildings to give variety and color. The pink, blue, and green tiles of the Spaniards are restful to the eye and attractive but, as they require frequent cleansing, are an item in upkeep.

Termites and Other Insects Destructive to Wood.—Extreme care must be taken to prevent white ants from infesting buildings. The Department of Health, Commonwealth of Australia, gives the following measures for their control:

(1) Regular inspection underneath buildings raised on stumps, the examination of each stump cap and ant stop for the earthen tunnels which show the track of white ants, the examination of the sills of buildings which are erected on concrete foundations, and close inspection inside. Boards in which white ants are working yield a hollow sound on tapping them with the knuckles. The gnawing of white ants in infested timber can sometimes be heard, especially on a still night, from inside a building.

(2) Examination of any pipes or other uncapped communication between the ground and the building. Where a pipe is brought up alongside a wall, the protected side requires close attention.

(3) Roof spaces should be examined at intervals with a lantern.

(4) Dead timber should be removed from the vicinity of buildings. An old stump or a neglected heap of firewood encourages white ants. Pieces of timber left leaning against a wall may enable white ants to enter.

(5) If white ants are found in a building, no time should be lost in dealing with them. The tunnels should be broken away as far as they can be reached, and white ant solution applied freely to them and to the surrounding wood. The extent of infestation should be traced out, and care taken that no other means of access is left.

(6) Posts attacked by white ants may be treated by boring an augur hole diagonally downwards, filling it with white ant solution, and refilling so long as the solution soaks into the wood. When full of the solution, the hole may then be closed with a wooden plug. In addition, the earth can be loosened up round the post with a bar and the solution poured down the side of the post.

(7) A good white ant solution may be made as follows:

Mix 2 lb. commercial arsenic with 1 lb. commercial caustic soda, both in the dry condition. Use a stick for mixing. When thoroughly mixed, add water and stir up into a paste. A good deal of heat will be evolved when the water is added. Keep on adding more water and stirring until the total added amounts to 2 gallons. Then boil for a few minutes, stirring meanwhile. When cool, strain through clean hessian or other suitable material to remove debris, and bottle and store for use. Label "White Ant Mixture—Poison."

Street's White Ant Cure is also efficient, and does not stain pine wood.

For coating posts or other woodwork before putting into the ground, the above-described solution may be used with good results in keeping off white ants and preventing rotting. Plymel will also serve well for this purpose, as will crude creosote, or the patent preparation Solignum.

Borers.—Borer beetles are liable to attack furniture and woodwork. Their presence may be detected by fine wood dust and bores of the size of a pin-hole or larger. They are capable of doing serious damage to floors, walls, or furniture and require careful attention. They will attack hardwood as well as pine. Treatment of the surfaces with the white ant solution will generally dispose of them. It requires care in application, being liable to damage certain kinds of surfaces. A good wetting with turpentine, applied to the infested surface with a brush, and re-applied if necessary, will give useful but not always certain results. Carbon bisulphide painted on is effective. It is inflammable in the presence of a light, and smells offensively before it dries.

Infested articles of smaller furniture may be cyanided. Painting infested surfaces will kill any borers in the wood, and will assist in preventing fresh attacks. During inspection of buildings and furniture, borer beetles should always be looked for.

Care of Living Quarters.—Of this, Balfour says: "The motto, 'where ignorance is bliss 'tis folly to be wise,' is not applicable to domestic hygiene in the tropics, and especially to the kitchens, their annexes, and the servants' latrines. Where regular inspections are carried out, natives soon learn that it pays to be cleanly; but it requires a great deal of energy and force of character to keep them up to the mark. Stables usually require a good deal of looking after, especially as regards the presence of 'fly nurseries' in them."

Air Conditioning

Artificial cooling of the air in tropical dwellings and in railway trains has long been practised. Its use in India has been well described by Megaw (1939). The method commonly employed there depends upon rapid evaporation of water from a "Khus-Khus" screen and upon drawing outer air through the screen and into the room to be cooled by means of a suction fan. Thus, a constant supply of cooled air is obtained. The method is effective only when the atmospheric humidity is low. If possible, the screen should be placed on the side of the house facing the prevailing wind. An exhaust fan can advantageously be used on the opposite side of the room. The entrance to the room should be through an antechamber provided with close fitting spring doors. Cooling of the air may also be promoted by spraying the floor with water or by hanging up sheets and keeping them wet.

Modern mechanical methods of "air conditioning" can now be used for cooling rooms or dwellings and for regulating humidity as well. There is a tendency, however, to maintain the temperature at too low a level. The result is that the room seems excessively cold to those who enter it and that, on returning to the outer air, they feel as if it were the breath of a furnace. Such extremes of difference are neither pleasant nor wholesome, especially when the skin or clothing is moist with perspiration. The optimal temperature differs so much as between individuals that it is impossible to set up a standard which will be comfortable for all persons.

With reference to information published by Yaglou (1937), it seems probable that the difference in temperature between the cooled room and the outer air should not exceed 15°F. and that a difference of 10°F. might be preferable. Yaglou said that dehumidification of air without much cooling is especially indicated in tropical climates and that it may prove the best method also in banks and stores where customers spend only a few minutes at a time. Similarly, moderate cooling of sleeping quarters would probably be advantageous where the nights are uncomfortably hot.

General use of mechanical cooling and dehumidifying devices is limited at present by their cost. Further research is needed also to determine how these devices can be used to the best advantage in the tropics.

Food Elements and Food Requirements

Foods include proteins, fats, carbohydrates, mineral salts, and water, but to sustain the body in health, they must be associated with vitamins and lipoids or nitrogenous fats. Of these, proteins, fats, and carbohydrates are nutrients. They are interchangeable within the body as sources of heat and energy, but proteins alone furnish material for growth and repair. Proteins increase metabolism more than do carbohydrates or fats.

Proteins.—These are very complex substances composed of nitrogen, carbon, oxygen, hydrogen, and sulphur. They are colloidal in character except in some leguminous plants, where they are crystalline. Proteins are essential for the maintenance of animal life because of the amino-acids which they contain. Many if not all of these amino-acids are essential for the building up and repair of body tissues. Only a few of them can be synthesized in the animal organism. Proteins vary greatly in biological value according to the different amino-acids that they contain and to the proportionate amounts of the more essential ones. Proteins differ also in digestibility. Even if no single essential amino-acid is totally lacking, as with certain proteids of some seeds commonly used as food, the proportionate amounts may be such that their utilization in the body is less complete than that of proteids of higher biological value. The greater the similarity of protein supplied to the tissues the higher is its value, hence the biological protein value of meat and milk is three to four times as great as that of maize.

In general, the proteins of animal foods have a higher nutritive value than those of vegetable origin. The proteins of meat, milk, and eggs, and those contained in glandular tissues such as liver, kidney and sweetbread, have an especially high nutritive value. "Of all natural foods milk not only comes the nearest to being a balanced food, for children particularly, but it contains in readily available form 18.7 grams of first-class protein to the pint (473.18 cc.), in addition to minerals, vitamins, carbohydrates, and fats." (Jones: 1939; p. 179.)

The same author (Jones: 1939) has emphasized the fact that the proteins of various legumes, including certain of the common kinds of beans, have a low nutritive value because they are comparatively indigestible and because they are deficient in cysteine. The contrary is true of the soy bean after it has been heated. In many cases, the digestibility of proteins is increased by cooking but some of the amino acids may be destroyed by exposure to a temperature much above that of boiling water.

Protein requirements, as they have been estimated, vary enormously. These estimates do not ordinarily take into account digestibility or quality with reference to content of essential amino-acids. Protein requirements depend largely upon circumstances. Severe labor, growth, pregnancy and lactation call for relatively large amounts of protein.

A daily protein intake of 50 grams is, probably, close to the minimum requirement, whereas lumbermen and athletes perhaps require 250 grams or more. Jones said (×1939; p. 183), "In practice the protein intake for all adults should not fall below 1 gram of protein per kilo of body weight, it should be derived from a variety of sources, and at least a part of it should be of animal origin." During growth, pregnancy and lactation, the requisites, according to Jones are approximately as follows:

Age (Years)	Grams per Kilo (2.2 Pounds) Body Weight
1–3	3.5
3–5	3.0
5–12	2.5
12–15	2.5
15–17	2.0
17–21	1.5
21 and upward	1.0
Women:	
Pregnant 0–3 months	1.0
Pregnant 4–9 months	1.5
Nursing	2.0

Studies of the diet of 1000 residents of New York, living apparently in normal moderate circumstances, showed that 60 per cent of them were taking diets yielding only 42 grams or even less of protein daily. It seems highly probable that careful examination of these individuals might have revealed evidence of malnutrition.

The healthy young adult in the United States, as represented by the average student of medicine, has seemingly become adjusted to a protein consumption not exceeding 80 grams daily. Chittenden advocated a low protein diet but the observations of McCay, Castellani, and others would seem to indicate that a greater protein intake than that recommended by Chittenden is necessary for the maintenance of good health in the Tropics. Du Bois said that very high protein diets cause hypertrophy of the kidney but that many investigators have found no evidence of nephritis.

The Eskimos, who for thousands of years have been living on an almost exclusive meat diet with very high protein content, seem to enjoy excellent health. According to Thomas, the Greenland Eskimo, living on a carnivorous diet, exhibits no increased tendency to vascular and renal disease. This diet furnishes him with vitamins adequate for protection against scurvy and rickets, while the Labrador Eskimo, who has abandoned his primitive methods of existence, whose meat is cooked, and whose diet includes many prepared, dried and canned articles, is very subject to both these maladies.

Carbohydrates are classified as monosaccharides, disaccharides and polysaccharides. The single sugars require no digestion and are absorbed directly into the blood stream. Three single sugars (monosaccharides) occur in foods or are formed from more complex carbohydrates in the process of digestion; i.e. glucose, or dextrose; fructose, or levulose; and galactose. Until converted into these single sugars, carbohydrates cannot be utilized by the body. Thus, the disaccharides, sucrose (cane or beet sugar), maltose (malt sugar) and lactose (milk sugar) are broken down by the action of enzymes before being absorbed. Maltose is an intermediate product in the digestion of starch, which is a polysaccharide (Mitchell: 1939).

Food stuffs containing carbohydrates, or starches and sugars, are represented by the tubers such as potatoes and yams, the sugars of the cane, beet, fruit and honey, and glycogen in muscle. The sugars, including candy, starch, and honey, consist almost entirely of carbohydrates, and, with the possible exception of honey, are lacking in all of the vitamins. The excess of carbohydrate is stored in the liver and muscles as glycogen. Glucose can be derived from the constituents of protein. A certain minimum percentage of glucose in the blood is indispensable for the maintenance of health. The above mentioned carbohydrates are the main source of heat and energy, are more

easily absorbed than any other class of food, and are essential for the proper combustion of fats.

The carbohydrate cellulose, forms the fibrous framework of vegetables. It is the chief constituent of wood, stalks and leaves. It has little if any food value for man, except that tender shoots and young leaves may, perhaps, be digested. Cellulose aids the digestion, however, by forming most of the residue which serves to stimulate the peristalsis of the bowels.

The hemicelluloses, agar-agar and pectin, are closely related to cellulose. They absorb water and promote action of the bowels by their bulk. On the other hand, pectin as contained in scraped, raw apple, has a beneficial action in diarrhoea.

Fats.—These are compounds of glycerin and fatty acids. Like carbohydrates, they are composed of carbon, hydrogen, and oxygen. They are represented by butter, the fat of meat, and a large number of vegetable oils obtained from nuts and seeds such as olive, cocoa-nut, and cottonseed oils. The fats serve as fuel and yield about twice as much energy in the form of heat and muscular work as an equal weight of carbohydrate or protein.

When an excess of fat is taken by sedentary persons, part of it is stored in the body where it yields no heat until oxidized.

Lipoids of nitrogenous fats are indispensable though their exact use is unknown. Sundstroem said that a single experiment in which the diet was exceptionally rich in lipoids indicated that such a diet was instrumental in raising the lipoid phosphorus level of the blood and that it suggested a method of treating the hypolecithinaemia, which, apparently, is common in tropical residents, notably in women and growing children. Experiences have been reported by tropical practitioners which emphasize the usefulness of lecithin as a curative agent in cases of debility and tropical "staleness."

Because of their relatively slow absorption, fats increase the "staying power" of a meal. They also add flavor to food and some of them are important for their content of the fat-soluble vitamins: A, D, E, and K. Lease (1939) said that there is little basis for the claim sometimes made that hydrogenated fat is better in human nutrition than natural fats; and that completeness of digestion is practically the same for all fats having melting points below body temperature.

Energy Requirements

Food serves as the fuel which supplies the energy required by the activity of the organs and muscles of the body. Heat is a by-product. Whatever the kind of food eaten, approximately the same number of calories are required for the performance of a foot pound of "work." The number of calories obtainable by the human body from different kinds of food differs greatly. Carbohydrates and fats can be completely utilized after digestion and absorption but a considerable energy-bearing residue of protein is excreted chiefly in the urine and to a less extent in the faeces. On a mixed and ample diet, there is some loss also of carbohydrates and fats. The physiological fuel values per gram for protein, fat and carbohydrates are respectively: 4, 9, and 4 calories (Morey: 1939). The caloric intake required for men and women in the United States differs in relation to height weight and occupation. Sedentary workers require less than do those who are performing physical labor. Thus, estimates for men range from 3000 to 4,700 calories per day; and those for women, from 2,200 to 3,300. The requirement for a women may be increased to 3,500 during pregnancy or lactation. The requirements for growing children per kilogram of body weight fall from about 100 calories in the first year to about 50 calories at the age of nineteen.

Condiments.—Among condiments are classed spices, coffee, and tea. They have no nutritive value except for the added sugar and cream but form an important adjunct to the dietary of both foreigners and natives in the tropics. By imparting flavor to many tasteless articles of food, they promote appetite and stimulate digestion.

Inorganic Substances.—Mineral salts are of the greatest importance in the formation of bone and assist in digestion and metabolism. While they are not ordinarily classed as foods, they are essential to life and include phosphorus, sulphur, potassium, sodium, calcium, magnesium, iron, chlorine, and iodine. They contribute primarily to

the supporting framework of body, are included in the formation of many organic compounds, and, as every cell contains mineral elements, form an integral part of the cell structure. They also circulate in the body fluids in various combinations such as inorganic salts, as dissociated ions, and in more or less loosely bound organic combinations. In this way the mineral salts of the plasma serve to maintain the osmotic tension necessary to life and are determining factors in neutrality regulation. Even closely related elements, such as sodium and potassium, exert their individual influence; some are antagonistic toward others and some are synergistic. It has been shown that the ingestion of large quantities of potassium, as in a vegetable diet, causes depletion of the sodium reserve of the body and the resulting urgent need for more sodium in the form of common salt as is experienced by herbivora. A more beneficial effect is exerted by calcium. In addition to the synergistic influence which this element exhibits toward iron, Meltzer and Auer believe that it is able to correct inorganic imbalance in either direction, that it nullifies the deleterious influence of sodium, potassium, or magnesium and thus is capable of re-establishing normal equilibrium.

The animal organism is capable of utilizing inorganic compounds of sodium, potassium, calcium, magnesium, chlorine, iodine, phosphorus and iron, when no other sources of these elements are provided. The various foods which are ordinarily found in the diet leave a residue or ash when metabolized which may be "acid forming" or "base forming." Although the healthy animal is remarkably capable of maintaining the normal hydrogen ion balance, the normal diet probably should contain sufficient alkaline ash foods to balance the acid ash foods. Most people on unrestricted diets form the habit of balancing such acid-forming foods as meat, eggs, and white bread with base-forming fruits and vegetables.

Requirements for most, if not all of the inorganic substances, are greatly increased during growth, pregnancy and lactation.

Carbonic, phosphoric, and sulphuric acids are continually being produced in metabolism. Under normal conditions, sugar, starches, fats, and portions of the proteins are burned to carbonic acid which is eliminated by respiration as CO_2. Sulphuric acid, a strong mineral acid, while readily fixed by proteins, is formed when the protein is resolved by hydrolysis into its constituent amino-acids and must be disposed of eventually by neutralization and excretion by the kidneys. Fruits and vegetables in general furnish bases capable of effecting neutralization. Henderson has stated that neutrality is a definite fundamental and important characteristic of the organism. Foods in which acid-forming elements predominate increase the acidity of the urine, increase urinary ammonia, and lessen the power of the urine to dissolve uric acid, which, not being destroyed, must be excreted as such. As Sansum has stated, foods that produce an acid ash result in a type of acidosis which produces sour taste, sour perspiration, sour urine, and sour disposition.

Calcium.—Lime constitutes about 2% of the body weight or a greater proportion than any of the other inorganic elements. Sherman (1939) stated that the ordinary mixed diet of Americans and Europeans living in cities and towns is probably more often deficient in lime salts than any other chemical element. He concluded that food for an adult or for a child should furnish at least 1.0 gram of calcium per day. German authorities place the daily requirements for man as about 1.5 grams as calcium oxide or 1.07 grams of calcium, according to Lusk, who quotes Tigersted's statement that the diet of Finns contains between 2 and 6 grams of calcium oxide daily. The average adult, therefore, should take in his food daily not less than 1 gram of calcium.

Sherman advised that more attention should be given to the choice of such foods as will increase the calcium content of the dietary.

The most practical means of insuring an abundance of calcium in the dietary is to use milk freely as a food. As fresh milk of good quality is rarely obtainable in the tropics, this element must be supplied by canned or dried milk or other foods which are the principal sources of calcium in utilizable form, such as eggs, spinach, cauliflower, peas, beans, string beans, carrots, parsnips, turnips, cabbage, lettuce, apples, pineapples, and the citrus fruits. McLaughlin has compared the calcium balance of a diet in which spinach supplied a very high proportion of the calcium with that of the same diet in which milk furnished an equal proportion of the element. The results were

secured to the concrete cover and equipped with a flange to prevent drainage back into the well, or when this is not practicable, by means of compressed air. The casings of deep or artesian wells should be constructed with watertight joints in much the same manner so that surface pollution will not be carried into the well. As well water keeps better in the dark protected from the outer air, ventilation of wells is not necessary.

(g) *Springs* are the surface outlets of ground water and may or may not be safe depending upon the character of the ground water. The source should be protected by an impervious covered concrete basin discharging by gravity through a pipe. Butler (1928) states that crystal clearness of spring water is not necessarily an index of its potability. A sparkling clear water may be heavily infected and thereby dangerous to those who drink it. The results of bacteriological examination of many springs in Haiti showed heavy contamination with faecal bacteria. He also states that in some tropical countries the calabash or gourd-like fruit of the calabash tree, the larger specimens of which have a capacity as great as eight liters, is used by many natives to carry water. As used, the calabash cannot be filled without contaminating the water by human hands. The calabash is carried by natives by inserting a finger into the filler opening thus contaminating the water a second time. Water cannot be sterilized by legitimate amounts of chlorine or iodine introduced into a calabash before it is filled. Bacteriological tests show that the entire dosage of these chemicals is absorbed or neutralized by the organic matter of the calabash itself without any disinfecting action which can be detected on the contained water.

Water Requirements.—A generous supply of water is desirable but at the same time unnecessary waste should be discouraged. The daily requirement per capita varies greatly and depends both upon the sanitary arrangements and the habits of the individual. It is stated that the average amount per person per day for domestic purposes is about 17 gallons. Of this, 3 pints are used for drinking, 3 pints for cooking, 5 gallons for bathing, 6 for washing, and 5 for sanitary purposes. (Three pints for drinking should be regarded in the tropics as a minimum.) Figures for some European towns which have a metered supply show a daily per capita consumption varying from 6.6 gallons for the poorer class of dwellings to 59 for the highest class of dwellings. In most cities of the United States the figures vary from 37 gallons per capita per day to 250, while in Calcutta it is stated that 40 to 50 gallons per person must be supplied daily.

Dual Water Supplies.—A double supply of water, one of doubtful purity for general purposes and one of unquestioned purity for personal use, is mentioned only to be condemned. Even where the community served is intelligent and careful the danger is very great. Where local conditions make this obligatory, the water for general purposes should be denatured. This may be accomplished through the use of sea water or overchlorination sufficient to make it unpalatable. The latter course would render it harmless so far as infections are concerned.

Water Purification.—In general, the methods of purification are natural, physical, mechanical, and chemical.

1. *Natural Methods.*—Nature's methods of purifying water include the self-purification of streams, storage, and sunlight. In the tropics, the probability of frequent contamination from native sources renders natural methods so unsafe that no dependence should be placed upon them.

2. *Physical Methods.*—Methods which include boiling and distillation, render the water flat and unpalatable though this can, to a certain extent, be overcome through aeration by shaking vigorously in a partially filled container. If left exposed to the air overnight, with due precautions against contamination, sufficient air will be taken up to remedy this defect. Boiling has the advantage of killing animal as well as vegetable life and, moreover, boiled water is readily obtainable in countries where tea drinking is habitual. If placed in clean bottles in the evening and the openings protected by plugs of cotton or covered with gauze, the water will be cool and palatable by the following morning. It is desirable, when traveling in the tropics, to carry a supply of boiled water from one camp in order to insure a supply of pure water upon arrival at the next.

3. *Mechanical Methods.*—Sedimentation and filtration are the usual mechanical means of purifying water, and are generally combined with chemical methods. The

domestic filter as ordinarily used in the household has a very limited sanitary value. Of the filter candles, Balfour recommends only the Pasteur-Chamberland and the Doulton. Domestic filters need to be sterilized by boiling every third day, as otherwise bacteria appear in large numbers in the filtrate. They must never be left to the care of native servants.

Filtration of public water supplies is accomplished, usually, by means of sand filter beds, either in the form of slow sand filters or in smaller units or tanks, the so-called mechanical or rapid sand filters.

(a) Slow Sand Filtration.—These filters consist of large, shallow, tight, underdrained reservoirs containing stratified filtering material of progressive degrees of fineness, from broken stone or gravel at the bottom to an upper layer of fine sand. They require an extensive tract of land and while the original cost is large the maintenance cost is comparatively small. Sedimentation is necessary to prevent rapid clogging of the filters. If the water contains much fine silt, preliminary chemical coagulation may be required. The water passes slowly through the sand and is collected in drains placed under the filter bed.

The process is mainly a biological relation and partly a mechanical straining. The bacteria, algae and other microorganisms form a gelatinous growth coating each grain of sand in the surface layers. This growth constitutes the *schmutzdecke* which effectively holds back the bacteria in the water. The action is uniform, removing about 99% of the bacteria and one-third of the coloring matter.

(b) Mechanical Filters.—Mechanical filtration requires the addition of a chemical coagulant, usually the sulphate of aluminium, alum or iron, to the water. Calcium carbonate is necessary to produce coagulation, and if not present in sufficient quantity, lime salts must be added. The amount of the coagulant must vary in accordance with the turbidity, the reaction, and the amount of calcium in the water. After passing through sedimentation reservoirs or tanks, where a large amount of the coagulated matter and bacteria are deposited, the water is passed rapidly through the sand filters where the straining process removes the suspended particles remaining in the water. The filters are cleaned frequently by reversing the flow. These filters occupy a small area of ground but have a capacity per acre per day from 100 to 200 times that of the slow sand filters. The first cost is comparatively small but the maintenance cost is large. They are especially suitable for turbid waters containing silt and clay, removing nearly all of the dissolved coloring matter and from 95 to 99% of bacteria. Despite the approximately perfect removal of disease-causing microorganisms by sedimentation, coagulation, and filtration, under actual working conditions breaks may occur in the process of filtration. Therefore, there should be equipment for final chemical disinfection of all supplies. Many cities chlorinate the water as it leaves the filtration plant.

4. *Chemical Sterilization.*—An ideal chemical agent for the sterilization of water must be inexpensive, stable in composition, rapid in action, and non-poisonous without producing a disagreeable taste, odor or color. Better results will be obtained if the water is first clarified by coagulation, sedimentation, straining, or filtering. A number of substances have been utilized for this purpose among which may be mentioned potassium permanganate, sodium bisulphate, iodine, and chlorine. The latter is used in the form of: (*a*) Gas from cylinders applied directly to the water in pipes or inclosed chambers (dry feed) or by first dissolving in a small amount of water (wet feed). (*b*) Chlorinated lime. (*c*) Interaction of chemicals. (*d*) Organic chlorine compounds.

Potassium permanganate is rarely used as the action is feeble and uncertain and the color objectionable. It is of value in the removal of disagreeable odors by oxidation and is said to be particularly efficacious in the destruction of cholera vibrios.

Sodium bisulphate in tablets is effective in a dose of 15 grains to one pint of water. The purifying action depends upon the liberation of free sulphuric acid. This compound deteriorates rapidly and if used over an extended period of time or in any quantity is prone to have a decided laxative effect. Balfour states that the bisulphate forms soluble sulphates with certain toxic metals. It can be safely used in aluminum water bottles, but not those made from alloys containing copper. In iron containers it forms a thick brown sulphate which renders the water undrinkable.

Iodine. Hitchens (1922) emphasized the use of tincture of iodine in the dosage of one drop to a canteenful or approximately one drop to a liter to render water potable.

Chlorine is a potent germicide and the most useful of the halogens, as chlorides do not have the depressing action of iodides or bromides. Chlorine gas is formed by the electrolytic decomposition of salt solutions. The moist gas is dried and then compressed into a liquid in steel cylinders of about 100 pounds capacity. The method of disinfection by chlorine gas is extensively used in the United States, but in isolated communities cylinders are difficult to procure and other methods are usually found to be more readily applicable. Chlorinated lime made by saturating slaked lime with chlorine at ordinary temperatures is an excellent source of chlorine but has the disadvantage of being very unstable. The hypochlorites upon exposure to air deteriorate rapidly to the more stable and inert carbonates. It is therefore necessary that the substance be kept in air-tight containers and protected from light. The amount of hypochlorites is usually expressed as available chlorine which is the chlorine readily liberated from its combination as determined by the usual titration with sodium thiosulphate. The available chlorine in a fresh sample may be as much as 30 or even 35% but frequently a sample will show, less than 20%. Some samples kept under ordinary storage conditions have shown less than 10%.

Chlorinated lime is soluble in about twenty times its weight of water, leaving an insoluble residue consisting mostly of calcium hydroxide. Half a pound of chlorinated lime dissolved in one gallon of water makes a solution containing approximately 6% by weight of chlorinated lime representing about 2% of available chlorine. A clear solution of chlorinated lime may be readily obtained if the undissolved fraction be allowed to settle. Sedimentation of the insoluble portion may be assisted if precautions are taken to mix a sufficiently thin paste, otherwise a gelatinizing action takes place and greater difficulty in settling is encountered. One pound of chlorinated lime should never be mixed with less than one-half a gallon of water. A stock solution for the chlorination of water in the field may be easily prepared by adding one-half teaspoonful of chlorinated lime to a point of water. This solution should be freshly made from a good grade of chlorinated lime having a strong odor of chlorine. Specimens of chlorinated lime that are moist, caked, or lumpy are generally low in chlorine and therefore should not be used. Of this stock solution use one teaspoonful to a gallon of water, or 15 drops (about ¼ teaspoonful) to one quart and let stand at least 15 minutes. This gives a free chlorine strength of approximately 1.3 parts per million which is considered sufficient for ordinary clear water. In the absence of a solution to test for free chlorine or if there is doubt as to the strength of the hypochlorite, the usual field method is to add the hypochlorite solution until the water gives a slight taste or odor of chlorine.

Raw waters differ greatly with respect to the amount of contained organic matter and therefore vary in their capacity to form compounds of chlorine that have no disinfectant action. Some waters will require more chlorinated lime than others to insure the presence of free chlorine after 15 minutes contact. Relatively pure waters chlorinated to the extent of 0.5 to 1 part chlorine per million as a rule contain, 15 minutes later, from one-fifth to one-fourth of the amount added. If it is impossible to test for residual chlorine, a clear water may be assumed to require not more than 2 parts chlorine per million when, from available evidence regarding source, vegetation, and pollution hazards, it does not appear to contain an extraordinary amount of organic matter. If doubt exists whether that amount will insure the presence of free chlorine at the expiration of 15 minutes, chlorination had best be continued up to 3 parts per million.

The Lyster bag designed by Colonel W. J. Lyster, United States Army, may be found effective for tropical use. It has been found by the editor to be practicable and most valuable during a number of expeditions into the interior in a number of tropical countries. It holds 36 gallons and consists of a canvas bag sewn to a galvanized iron ring hinged so that when the bag is empty it can be folded to occupy very little space. Two crossed pieces of rope are attached to four equidistant points on the ring allowing the bag to be suspended when in use. Five nickel plated spring self-closing faucets are placed at equal spaces just above the bottom edge of the bag. Water is treated in the bag as follows:

(a) Set up bag, adjust the cover, and strain in the water to within about 4 inches of the top.

(b) Obtain a clean stick or some other device for stirring the water. Place the stick in the water and let it stay; do not take it out of the water.

(c) Place 1 gram of chlorinated lime in a canteen cup; stir the powder with water, making a paste first, and then add enough water to dissolve all of the soluble powder. Pour the contents of the cup into the bag. Be sure the chlorinated lime used has not deteriorated. It should be dry and give off a pronounced odor of chlorine. If available and in good condition, brown glass tubes, made for the purpose, each containing 1 gram of calcium hypochlorite, may be used gram for gram instead of chlorinated lime from some other supply. As used, calcium hypochlorite on the labels means chlorinated lime.

(d) After adding the chlorine, stir the water in the bag thoroughly and allow the water to stand 15, or preferably 30, minutes before using. At the end of the 15 or 30 minutes contact period, add sodium hyposulphite, if available, in the proportion of 1 gram to 2 grams of chlorinated lime. Again stir the water thoroughly and wait a few minutes before using.

(e) If an orthotolidin testing solution is available, it may be used to test for the presence of free residual chlorine in the water after a 15-minute contact period. The dosage of chlorinated lime (calcium hypochlorite) may then be regulated so that only enough is added to satisfy the affinity of organic matter present and leave a small amount of free chlorine (residual chlorine) at the end of 15 minutes' contact—0.2 parts per million or less.

(f) Sodium thiosulphate (hyposulphite) combines with free chlorine and removes the odor and taste resulting from the presence of the latter. A tube containing 1 gram of sodium thiosulphate, made for the purpose, is broken into a canteen cup filled with water; the crystals are shaken into the water, which is then stirred with a spoon and allowed to stand for 30 minutes. The solution is poured into the Lyster bag, and the contents are again thoroughly stirred with the stick which has been left in the bag. To make certain that the faucets have been flushed with the excessively chlorinated water, 5 cupfuls should have been run through each faucet and poured back into the bag, five to ten minutes before adding the solution of sodium thiosulphate. The water is now ready for drinking.

(g) If scales are not available, 1 gram of chlorinated lime, if dry, may be quite accurately measured with an empty Colt .45-caliber cartridge shell which holds about 1 gram if filled level by pouring in without packing down in any manner except by lightly tapping the shell once or twice.

The effect of halazone, which is p-sulfone-dichloramidobenzoic acid, depends upon the liberation of free chlorine for its germicidal action. This compound can be purchased in tablet form (p. 1703). When protected from moisture, it is remarkably stable even under tropical conditions.

Sewage Disposal

Sewage may be defined as solid and liquid excreta combined with other solid and liquid wastes from houses and other buildings, diluted with the water used. The basic principle according to Whipple is the disposal of sewage as soon as possible with the least nuisance to the smallest number, with the least damage to health or property and at the lowest cost. Improper disposal may have a direct effect upon health by transmission of disease or may create nuisances both objectionable and offensive. The simplest method is found in cities provided with water and sewer systems where the sewage is discharged into large bodies of water and disposed of by dilution with subsequent natural purification. In most tropical locations where this method is not feasible recourse must be had to other methods.

The privy is the simplest method for the disposal of human excreta. They are generally classed as ground, pail, earthpit, deep post-hole, concrete vault, chemical and septic privies. In all types, the access of flies to excreta should be prevented through

tight construction and by keeping the seat covers closed. This may be accomplished by small blocks placed at the back of the seats which will automatically cause them to fall shut when not in use.

The Pail Privy.—In some small communities provided with a satisfactory scavenger service, this type may be used with success. The pail privy is built on top of the ground and is constructed with a tight-fitting hinged cover at the rear, with pails placed under the seats. When the pails are about three-fourths full, they are removed by the collector, covered for transportation, and the contents disposed of by burial in shallow trenches away from sources of water supply. The pails are then cleaned and disinfected.

The Lumsden, Roberts, and Stiles Privy.—This is a simple and inexpensive apparatus for use in the safe disposal of night-soil and operates upon the principle of the septic tank. It consists of a water tight tank, barrel, or other container to receive and liquefy the excreta. A covered water tight can or other vessel to receive the effluent. A connecting pipe about 2½ inches in diameter and about 12 inches long; the end in the receiving chamber is provided with an open T, both openings of which are covered with wire screens. A tight box, preferably zinc lined, which fits tightly on the top of the liquefying barrel. It is provided with an opening on top for the seat which has an automatically closing lid. An antisplashing device, consisting of a small board placed horizontally under the seat about an inch below the level of the transverse connecting pipe. It is held in place by a rod which passes through an opening in the side of the seat and by which the board is raised and lowered. A layer of chips floated in the tank may be used in place of this device. A ventilating pipe connects the space under the seat with the open air.

The liquefying tank is filled with water up to the point where it begins to trickle into the effluent tank. A pound or two of old manure should be added to the water to start fermentation. A film of some form of petroleum should be poured on the surface of the liquid in each container as an insect repellent.

When the privy is to be used, the rod is pulled up so that the antisplashing board rises to within about an inch of the surface. As the faecal material falls into the water the board prevents splashing. Although some of the excreta floats it is protected from flies by the automatically closing lid, by the water, by the film of oil, and lastly by having the apparatus in a thoroughly screened out building which should be done for additional safety. The film of oil prevents mosquito breeding in the tank.

The faecal material ferments in the water and gradually liquefies. The level of the liquid is raised and the excess flows into the effluent tank, where it is protected from insects by the cover and by a film of oil. This effluent may be allowed to collect until it reaches the level of the connecting pipe, when it may safely be disposed of by disinfection and burial.

The Septic Tank.—The purpose of a septic tank is to digest and liquefy a large percentage of the suspended solids but does not necessarily purify the sewage. It may be possible in some instances to secure dilution sufficient to omit treatment of the septic tank effluent by discharging the overflow into streams with a large flow at all times. The effluent from a septic tank may contain large numbers of harmful bacteria and may have a foul odor. It is stated that odors from the septic tank installed at the U. S. Marine Corps Brigade Hospital, Haiti, are prevented by the weekly addition of a small amount of fresh horse manure. Disinfectants and chemicals which may destroy bacteria interfere with proper digestion of solids and should not be discharged into septic tanks. Rain and surface water does not need treatment, cause an undue load, and should be diverted from the tank. Septic tanks are easily constructed of concrete and if well built operate satisfactorily. Solids accumulate and should be removed at intervals, usually from two to four years, depending on the capacity of the tank and the size of the contributing population.

The design of septic tanks should allow for sufficient capacity. Capacity refers to the amount of liquid that may be retained below the bottom of the outlet pipe and not the total volume. For residences the liquid capacity varies from 325 gallons for 5 persons to 1500 gallons for 30 persons. Inlets and outlets should be arranged so as to avoid stirring up the contents unduly, which would interfere with sedimentation, and

increase the probability of clogging. Access by manholes or by removal tops must be provided for cleaning purposes.

The effluent from septic tanks is usually disposed of by soil absorption from cesspools or by seepage from underground porous tile drains. Sewage disposal units must be located so that seepage cannot reach any water supply under varying conditions of soil or underlying rock and ground water. In general they should be located as far away as practicable and never on a direct slope toward wells, springs, or other water supplies. It should be borne in mind, however, that water supplies may become polluted through variations in the level of the ground water or through peculiar underlying geologic formations, even though sewage disposal units are located at lower surface levels.

Noxious Arthropoda

Flies.—Many diseases, expecially those transmissible by discharges from the intestinal tract, are spread by means of food, fingers, and flies with human faeces as the source of the infective material. Howard (1926) states that collections of flies from dining rooms in different parts of the United States indicated that the true house fly comprised the greatest number. Other species observed were the biting stable fly and the cluster fly. Several species of metallic greenish or bluish flies were also found occasionally. These include a blue-bottle fly, the black blow flies, and the green-bottle flies which breed in decaying animal matter.

Carriers of Disease.—The true house fly which is found in nearly all parts of the world prefers to deposit its eggs in horse manure. It will also feed on and breed in human excrement, and because of this habit is dangerous to the health of human beings. The fly may carry on its body the causative agent of intestinal diseases such as typhoid fever, dysentery, and cholera from the excreta to food supplies, or deposit various microorganisms in its excreta. Wenyon has shown that the *E. histolytica* ingested in the encysted form may be passed in the faeces 24 to 40 hours later. In the case of over 30 different disease microorganisms and parasitic worms, actual laboratory proof of transmission exists and where lacking, is replaced by circumstantial evidence amounting almost to certainty. The house fly has been found to breed freely in hog manure and, to some extent, in cow manure. In fact it will, when necessary, lay its eggs on a great variety of decaying vegetable and animal material. Dunn has stated that in Panama a fly may deposit as many as 2367 eggs in 21 groups, and sometimes an interval of only 36 hours may occur between the deposition of large numbers of eggs.

Power of Emergence from the Soil.—A few hours before pupation the larvae migrate from their feeding ground in search of a favorable place in which to pass the pupa stage. They may crawl considerable distances from the place of their origin to pupate in the ground or in other loose material. The adult fly, upon emerging from the puparium, works its way upward to the surface. Wallace states that the newly hatched fly is able to accomplish this through the inflation and deflation of a frontal sac attached to the head between the eyes. Experiments showed that house flies on emerging from the pupae were able to penetrate a covering of 6 to 7 inches of garden soil and a double layer of 2 mm. mesh mosquito netting. Passage through the netting was made by inserting the sac within the mesh and then inflating. With expanding of the wings, in final development after exposure to air, the capacity for inflating the frontal sac is lost.

Fly Papers and Poisons.—The use of sticky fly papers in the destruction of flies is well known, and fly poison preparations are common. A very effective fly poison is made by adding 3 teaspoonfuls of commercial formalin to a pint of milk or water sweetened with brown sugar. A convenient way of exposing this poison is by partly filling an ordinary drinking glass with the solution. A saucer or plate is then lined with white blotting paper cut the size of the dish and placed bottom up over the glass The whole is then quickly inverted and a small match stick placed under the edge of the glass. As the solution evaporates from the paper more flows out from the glass and automatically renews the supply.

Fly traps may be used to advantage in decreasing the number of flies not only for immediate results but because of the chance that they may be disposed of prior to ovi-

deposit. Experiments with marked flies showed that the house fly may travel as far as 11 miles in 4 to 7 days. Some flies were caught as far as 17 miles from the point of liberation. The length of flight indicates the necessity for using traps as well as control of local breeding places. An effective, inexpensive and serviceable trap may be made with four wooden barrel hoops, one barrel head, four laths together with the necessary wire mesh screening. The trap consists essentially of a screen cylinder with a frame made of the barrel hoops and lath, in the bottom of which is inserted a screen cone. The height of the cylinder is 24 inches, the diameter 18 inches, and the cone 22 inches in height and 18 inches in diameter at the base. The effectiveness of the traps will depend upon the selection of baits. A good bait for house flies is 1 part of molasses to 3 parts of water, after the mixture has fermented for a day or two. Overripe or fermenting bananas give good results, likewise a mixture of equal parts of brown sugar and curd of sour milk thoroughly moistened after it has stood for three or four days.

Prevention of Fly Breeding.—The most logical method of abating the fly nuisance is the elimination or treatment of all breeding places. The destruction of adult flies is at best only a temporary expedient. It is advisable that all manure be placed, when practicable, and as soon as possible after it is voided, in fly tight pits or bins constructed preferably of concrete. The essential point is that flies be prevented from reaching the manure before it is placed in the container. This frequently happens and flies emerge before the container is emptied. To obviate the escape of newly hatched flies, openings large enough to attract flies to the light may be made in the cover and the openings covered with ordinary conical traps arranged so the bottoms of the traps will fit closely to the cover.

Chemical Treatment of Manure.—With the object of finding some cheap chemical which would be effective in destroying fly larvae without reducing the fertilizing value, the Bureau of Entomology conducted a series of experiments with a number of chemicals. Of the substances tried powdered hellebore gave excellent results. A watery extract, prepared by adding one-half pound of the powder to 10 gallons of water and allowed to stand 24 hours, is then sprinkled over the manure in the proportion of 10 gallons to every 10 cu. ft. This treatment results in the destruction of 88 to 99% of the larvae. It is, however, somewhat poisonous to live stock.

Another chemical even more effective as a larvicide is powdered borax. The minimum amount necessary to kill fly larvae was found to be one pound to 16 cubic feet. In this proportion 90% of the larvae were destroyed and heavier applications killed from 98 to 99%. Best results were obtained when the borax was applied in solution or when water was sprinkled after the borax had been scattered evenly over the manure. Applied in the latter manner one-half pound of calcium cyanamid and one-half pound acid phosphate per bushel of manure gave an apparent larvicidal action of 98%.

Trap for the Destruction of Fly Larvae.—This method is based on the fact that larvae of the house fly show a strong tendency to migrate a few hours before pupation. The manure is placed upon a slatted platform which stands about 1 foot above a concrete floor. A rim of concrete 4 inches high and integral with it surrounds the floor which is sloped toward one corner. From this corner a pipe leads to a small cistern nearby. The pipe is stoppered and the concrete floor filled with water to a depth of one inch in the shallowest part. When the larvae migrate they drop into the water, are drowned, and subsequently washed into the cistern. The platform beneath must be kept free of accumulations of manure, and moisture applied regularly to the pile to drive the larvae out

Compact Heaping.—Another method recommended by English writers consists in building the manure in a compact rectangular heap the sides of which are beaten hard with shovels. Loose straw is placed around the pile about 1 foot from the edge. The exclusion of air together with the higher temperature and gases formed by fermentation tend to make conditions unfavorable for the development of fly larvae. Those which do develop, migrate and pupate in the straw surrounding the heap where they may be destroyed by burning. In large camps during the World War manure was closely packed daily and the surface thoroughly drenched with an emulsion of crude tar oil and soap in the proportion of 1 gallon per square yard. It was found necessary in conjunc-

tion with this method to attempt concurrent destruction of the adult flies. Accordingly oil drums were turned on end and a solution of 1% of sodium arsenite in water containing 12% glycerine and 5% sugar was poured in the saucer-like depression in the top. The flies collected in masses and were killed in enormous numbers.

While horse manure produces the greatest number of flies, breeding in other material should also be prevented. Garbage and other organic matter must be placed in fly-tight containers until collected and all decaying vegetable and animal matter must be properly disposed of by incineration or burying.

Sprays.—An efficient insecticide for flies, cockroaches, moths, ticks, bedbugs, some species of ants, and many other insects may be easily prepared by mixing pyrethrum flowers with kerosene, turpentine substitute, or other similar hydrocarbon oil in the proportion of 1 pound of pyrethrum, the powdered or coarsely ground flowers may also be used, to 1 gallon of the oil. The mixture is allowed to stand two to three days and then percolated once. One percolation removes about 95% of the active principle. The resulting solution if sprayed directly on the insects has a paralytic action and causes death within a few minutes. In the case of cockroaches and bedbugs, which are nocturnal in their habits, it may be applied in the evening freely to the places frequented by them.

"Flit" and various similar proprietary sprays are very effective against flies and other insects but their use is limited by expense.

Mosquitoes.—Measures for the control and destruction of mosquitoes involve the elimination of breeding places by filling; drainage, both surface and sub-surface; introduction of sea water into areas of fresh water; trimming and cleaning of banks of streams and lakes; cutting of brush and grass together with the elimination or screening of any formation, natural or artificial, capable of holding water such as rain-barrels, cisterns, pails, hoofprints, hollow trees, plants, gutters, orange peels, tin cans, and empty bottles.

When drainage, filling, and the use of fish are not practicable various larvicidal agents may be employed. The most common of these are petroleum, both crude and refined, old crank case oil diluted with 5 parts of kerosene and 1 of castor oil, crude phenol, cresol, Paris green, and the so-called Panama larvicide. The latter which was successfully used by Mason is compounded as follows: Add 200 pounds powdered resin to 150 gallons crude phenol. Heat mixture to 212°F. until uniform liquid is obtained. Dissolve 30 pounds caustic soda in 6 gallons of water and add to mixture, stirring briskly. Keep at boiling point until a sample immediately emulsifies with water. The larvicide in a 1 to 1000 emulsion kills mosquito larvae in one to five minutes; in a 1 to 5000 emulsion in 30 minutes. Sprinkled upon the water in a 10% emulsion so as to form about a 1 to 2000 solution, it spreads rapidly through the water and kills all larvae with which it comes in contact. The larvicide should not be used with oil or to dilute oil as the soapy characteristics interfere with satisfactory filming. Efficacy is impaired by exposure to air. Costs 25 to 30 cents per gallon.

Barber and Hayne found Paris green effective in destroying anopheline larvae. The application of insecticidal dusts by aeroplane was first demonstrated by the Army Air Service in cooperation with the Ohio State Experimental Station in August, 1921 and excellent results have been obtained in the United States in the distribution of Paris green by this method.

Experiments conducted at Quantico, Va. in 1926 showed the effective quantity of Paris green to be one pound per acre. Flying at an altitude of 100 feet or less, a 25% mixture with powdered soap stone or hydrate lime was effective. In winds of greater velocity and at altitudes greater than 100 feet a 50% mixture was required. Material costs about 70 cents per acre per season. Road dust, sand, ashes, flour, sawdust, and other materials have been mentioned as satisfactory diluents. In treating small areas good results have followed the use of a 1% mixture of Paris green in road dust distributed by a hand machine such as the Champion dusters. Griffitts found that a mixture of wet sand and Paris green is apparently lethal to sub-surface as well as surface-feeding mosquito larvae. Local conditions, however, determine the methods which will give the best results in each locality. The use of Paris green-dust mixture was found to be

of little value in Panama not only on account of the difficulty in keeping the mixture dry during the long rainy season but because most of the powder would adhere to the moist surfaces of the vegetation and little of it would reach the surface of the water.

Many species of anopheles after becoming engorged with blood are so encumbered that they ordinarily do not fly for a considerable period of time but rest in suitable shaded places near the location where the blood meal was obtained. Darling has shown that about two and one-half days elapse after feeding before the blood meal is expelled. Recently engorged anopheles at rest are relatively easy to destroy. They may be collected on a layer of cotton in a bottle containing kerosene or chloroform, or in a Griffitt's catching tube. The ordinary fly swatter or the pyrethrum-kerosene spray noted above in the control of flies may be used to advantage. The former method, however, preserves the mosquito without mutilation for the purpose of identification. Thorough screening of buildings in malarious districts and segregation of foreigners far apart from native villages are important preventive measures. Repellants are poor substitutes for screening. Sprays are useful in enclosed spaces. See also p. 1744.

The Bedbug.—This insect, which is nocturnal in its habits, has been recognized since the beginning of recorded history and, as a result of close association with man wherever he has gone, exhibits a considerable degree of caution, intelligence, and cunning in the selection of places of concealment during the day. The bedbug has been known to attack human beings in broad daylight though normally feeding at night or in the dark. While there is no convincing evidence that this insect is the usual vector of disease, it has been suspected in the transmission of kala-azar, tropical sore, European and African relapsing fever, Chagas fever of Brazil, tuberculosis, leprosy, and plague. Successful inoculation, if it occurs in these diseases, probably results from the accidental carriage of the causative agent on the mouth parts. Feeding requires from 5 to 10 minutes after which the insect retires to its place of concealment for the 6 to 10 days necessary for digestion and molting, or if in the adult stage, for ovideposit. During hot weather the eggs hatch in from 7 to 10 days. It may survive for a year and perhaps even longer without food. Distribution is commonly effected by articles ordinarily used by man such as clothing, laundry, and traveling accessories. Its habitats are cracks and crevices in furniture, buildings, ships, or cars. Balfour records that during a campaign in East Africa, bedbugs were found within the cork lining of helmets. At one camp, the helmets were deposited together at night and the infestation became almost general. The house centipede, cockroach, and the common red house ant are said to be natural enemies but are of little importance in the control of bedbugs.

Eradication.—A temperature of from 96° to 100°F. accompanied with a high relative humidity will kill newly hatched bedbugs within a few days, and 113°F. within a few minutes. The higher temperature will also destroy the eggs. Clothing and bedding may be exposed daily to fresh air and sunlight. Steam, hot water, and the blow torch are effective where they can be applied. A bag disinfector may be readily constructed of heavy canvas. The upper end should be permanently closed by sewing. A small opening should be made at the top for the introduction of the nozzle or end of a steam hose and the lower end arranged so that it can be closed sufficiently to at least partially confine the steam.

Simple methods of control consist of the liberal application of kerosene, benzene, or any of the lighter petroleum oils, either plain or containing 10% of crude cresol with or without the addition of turpentine, and applied with brushes or by injecting with syringes, into all crevices of beds, furniture, or walls, where the insects may be concealed. Corrosive sublimate is of value if a strong solution is used. The kerosene pyrethrum mixture is lethal within a few seconds, may be applied by brush, spray, or syringe, and is perhaps the most reliable liquid preparation.

Badly infested quarters may require fumigation. Hydrocyanic-acid gas, using 5 to 10 ounces of potassium cyanid per 1000 cubic feet with an exposure of one hour, is very efficient but must be intelligently employed on account of the danger to human beings. The fumes of burning sulphur destroy the insect in all stages, including the egg, and are of value where this method is not objectionable. The effective dosage

may be obtained by burning four pounds of sulphur for each 1000 cubic feet of space, with an exposure period of at least six hours.

Ants.—These troublesome insects may be destroyed by placing a ball of waste or cotton saturated with carbon bisulphide in the burrows in the ground and then carefully sealing the opening with moist clay.

Calcium cyanide in the form of granules or dust is said to destroy effectively land crabs and ants. On exposure to air, this material slowly reacts with the moisture of the atmosphere and gives off hydrocyanic-acid gas. The chemical is placed in the burrows and the openings sealed with wet clay. Precautions must be taken to prevent poisoning by hydrocyanic-acid gas in the storing and handling of calcium cyanide.

Other Arthropoda.—Fleas, see pages 700 and 1742. Lice, see page 1743. Sand-flies, see page 921. Scabies, see page 1493. Ticks, see pages 353 and 1734.

Control of Native Tropical Races

Whether or not he wishes, the white man in the tropics must come in contact with natives and especially those who work under his direction or who serve him. The following note made by Pearson and Monchet, regarding the correct attitude towards native assistants who are being trained, are applicable towards any natives and may be quoted here. "One can, indeed, tabulate the most important features of the attitude which will lead most quickly to the confidence of the natives as follows:

1. Maintain a quiet manner and never lose temper.
2. Be insistent as to obedience in all details. Never pass over a neglect of duty, however small.
3. Maintain reserve with natives. Do not chat with them about matters outside work. Never joke with them.
4. Be as considerate as possible, but never weak.
5. Never forget a promise, nor make one which you may not be able to keep."

While living in the tropics is generally supposed to be detrimental to the health of white people as compared with natives, statistics from several large cities located in the tropics or subtropics show that there is a wide difference between the death rates of foreigners and natives in favor of the white race.

Simple health rules published by the Bureau of Health, Manila, P. I. are quite to the point and may be observed without great difficulty:

"It is easier to maintain good health in the tropics than in the United States, but in order to do so you should observe the following simple rules:

Never drink any water unless it has been either boiled or distilled, nor eat any raw vegetables. If you observe this rule carefully you will probably never contract dysentery, typhoid fever, cholera, or any other disease that originates in the intestines. Disregard of this rule is responsible for the return to the United States of over 50% of the invalids who leave these islands.

Fruit is wholesome, and may generally be eaten raw with impunity, provided it is of a kind that grows upon trees, well above the ground.

Alcoholic stimulants are not necessary, the advice of 'old residents' to the contrary notwithstanding.

Generally, disease-carrying mosquitoes fly only at night; therefore, always sleep under a good mosquito net.

Finally, observe the same hygienic rules that are applicable to temperate climates, including those of physical exercise."

It may be added that the housing facilities should provide plenty of space, good ventilation, and be properly screened.

Venereal disease must be avoided.

No family should live in remote places where good medical care is not immediately available, as many tropical diseases are rapid and fatal in their action, especially in children. Yearly changes of residence to a cooler climate should be possible for both women and children.

In conclusion, it may be stated that the increasing demand for tropical products both for food and for industrial purposes requires the ultimate utilization by man of the fertile

Leukaemias.—Gradual painless enlargement of the spleen to an enormous size is characteristic of myeloid leukaemia, lymphatic leukaemia, pseudo-leukaemia infantum.

Malaria.—Splenic enlargement and tenderness are important points in diagnosis of malaria. In acute malignant tertian infections the spleen is often diffluent so that it is liable to rupture upon slight injury. The palpation of the spleen in acute malaria is a difficult procedure. Although it may be considerably enlarged, it is so soft that palpation is difficult. One should even exercise care not to palpate the spleen too violently and the possibility of accident should be thought of in making a spleen puncture. The typical malaria spleen is the ague cake of malarial cachexia. Here we have a greatly enlarged spleen with a thickened capsule and firm consistence. This spleen may fill up one side of the abdomen.

Malta Fever.—The splenic enlargement in this disease usually corresponds about to that of typhoid fever. At times, however, the size may be so great as even to suggest kala-azar.

Relapsing Fever.—Splenic enlargement and tenderness are marked features in this disease, often being noted early in the course.

Rickets.—The spleen may be readily palpable in rickets. The malnutrition, rachitic rosary, presence of Harrison's groove, projection of sternum, painful joints, craniotabes, enlarged abdomen, profuse sweating and tendency to atony is present. Blood chemistry shows reduction of inorganic phosphates.

Rocky Mountain Fever.—One point of distinction between spotted fever of the Rocky Mountains and typhus fever may be that the spleen of the former disease is usually enlarged three or four times the normal, while that of typhus fever shows no increase in size. The palpable spleen of Rocky Mountain fever is firm instead of soft as with typhus fever.

Schistosomiasis.—The spleen may be enlarged in Japanese schistosomiasis as well as in African schistosomiasis due to either *S. haematobium* or *S. mansoni.*

Splenic Anaemia.—(Banti's disease.) Enlarged spleen, leucopenia, recurring hematemesis and secondary anaemia. Must be differentiated from syphilis with anaemia accompanied by splenomegaly.

Syphilis.—In congenital syphilis the spleen is often enlarged along with the liver. In syphilitic cirrhosis of the liver the spleen may be greatly enlarged. Syphilis may be the cause of the same clinical and blood picture as found in Banti's disease. Syphilis may produce an anaemia associated with splenomegaly and every such case having a positive Kahn serum reaction should be regarded as luetic until proven otherwise.

Sprue.—This interesting disease may be diagnosed by: (1) Diarrhoea with the characteristic white stools, which may be intimately mixed with bubbles of gas giving them a frothy appearance. (2) Tongue and mouth lesions in which the tongue is denuded of epithelium and shows inflammatory changes. (3) Loss of weight. (4) Anaemia may be moderate to severe. The red blood count may fall to 1,000,000 per c.mm., and resemble the picture of pernicious anaemia. (5) Small liver. (6) The neutral fat and fatty acid ratio in sprue may become 1–5 against a normal of neutral fat 1, fatty acid 2. Sprue may simulate pernicious anaemia, pellagra, malignancy of the pancreas, syphilis, and dysentery. In malignancy of the pancreas the neutral fat and fatty acid ratio helps differentiate as in this condition the neutral fat in the stool may be as high as 15, to fatty acids 1. Pernicious anaemia, syphilis and dysentery may be differentiated by thorough laboratory study and the absence of true sprue stool differentiates pellagra. Sprue is now recognized as a nutritional deficiency disease. See p. 1023. See diarrhoea for etiology of tetany in fatty or chylous diarrhoea.

Stomach and Oesophagus.—Very important in diagnosis is a tenderness in the pyloric end of the stomach, which is brought out by attempting to palpate the epigastric region. It is often marked in yellow fever and acute pernicious beriberi as well as in blackwater fever and bilious remittent fever. We also frequently have epigastric tenderness, extending to the right, in ancylostomiasis. Hookworm patients are often "pot-bellied" and the craving for eating unusual articles, as earth, may be connected with the gastric hyperacidity which the patient desires to neutralize with alkaline earth.

Pellagra gives eructations and pyrosis and very common is a burning sensation extending from the stomach along the line of the oesophagus.

Deodorants may or may not be antiseptic or germicidal. An insecticide may or may not be a germicide and *vice versa.*

In disinfection we must consider:

1. Strength of solution. It must always be kept in mind that the strength of a germicidal solution when added to an equal amount of material to be disinfected is reduced in strength one-half. Thus 1 pint of a 5% compound cresol solution added to 1 pint of faecal material has a disinfecting effect of a 2.5% solution.

2. Time of application. A common mistake is to consider a few minutes as sufficient for contact of germ-containing material with the disinfectant. In the faeces-cresol mixture above noted the action of the disinfectant should continue at least one hour before emptying the vessel.

3. Nature of medium in which disinfectant acts. Germicidal agents are much less effective against bacteria contained in material rich in organic matter than when in pure water.

4 Temperature. Disinfecting solutions show greater power as the temperature rises, and act less efficiently in the cold. At 39°C., they are active.

By Coefficient of Inhibition we mean time and concentration necessary to prevent development of bacteria.

By Inferior Lethal Coefficient we mean time and concentration necessary to kill non-spore-bearing bacteria.

By Superior Lethal Coefficient we mean time and concentration necessary to kill spore-bearing bacteria.

Phenol Coefficients.—In determining the germicidal strength of a disinfectant against any given organism it is compared with that of phenol. The Bureau of Chemistry, Department of Agriculture, determines the phenol coefficients of disinfectants under the provisions of the Food and Drugs Act and the Insecticide Act. They are expressed as the *B. typhosus* phenol coefficient, *S. aureus* phenol coefficient, etc., depending upon the organism used in the determinations. If more powerful than phenol under the conditions of test the coefficient will be greater than 1. The method employed by the Bureau of Chemistry is based on the Rideal-Walker and the Hygienic Laboratory methods but differs from both in some respects.

Disinfectants May Be (A) Physical, (B) Chemical

(A) Of the **physical disinfectants** we have:

1. Sunlight. The red and yellow rays are practically inert, the ultra-violet most active. Direct sunlight kills non-spore-bearing pathogenic organisms in from one to several hours depending upon moisture, temperature and other conditions. Exposure equivalent to 30 hours sunlight is usually required to kill anthrax spores.

2. Burning is effective when practicable.

3. Boiling is efficient. Non-spore-bearing bacteria are killed almost instantly by a boiling temperature, but spores may resist destruction for many hours at 100°C. One must remember that the boiling point is lower at mountainous elevations.

4. Steam is extremely efficient when penetration is insured.

(B) Chemical Disinfectants.—*Bichloride of mercury* is usually sold in the form of antiseptic tablets. As a disinfectant for the infectious diseases it is usually used in a strength of 1–1000. The solution should be made in a wooden, enameled or earthenware vessel. As bichloride forms inert albuminates it should not be used in disinfection of sputum, faeces or any albuminous excreta. It must be remembered that bichloride is a mordant so that any stains in soiled clothing will remain permanent. For disinfection of clothing the material should be left in 1–1000 bichloride for one hour. Dishes for food should never be disinfected in bichloride on account of the danger from poisoning. Floors and walls may be disinfected with 1–1000 bichloride applied with a mop. Allow the solution to dry on the floor or walls.

Solution of formaldehyde, U.S.P., contains not less than 37% of formaldehyde. A 5% dilution in water (50 cc. sol. formaldehyde, 950 cc. water) makes a satisfactory disinfectant for soiled clothing. It is also valuable for albuminous material. The

disinfectant must act in a strength of 5% so that if 1 pint of faeces is to be disinfected we should add to it a 10% dilution of the official solution and allow it to act for one hour.

Fumigation with formaldehyde is employed only when the object is to destroy bacteria as the gas is valueless as an insecticide. Such fumigation is now seldom considered necessary in public health practice. Formaldehyde is efficient as a surface disinfectant when the temperature is above 50°F. and the air contains at least 60% of moisture. Owing to its lack of penetration the gas is not efficient for the disinfection of mattresses, or similar articles.

A convenient method of formaldehyde fumigation is to pour 500 cc. of Solution of Formaldehyde on 250 Gm. of barium dioxide or potassium permanganate for each 1000 cubic feet, allowing exposure for 6 to 12 hours.

In employing this method, take a pan partly filled with water. Place in this a second metal or glass receptacle containing the barium dioxide or potassium permanganate and pour in the Solution of Formaldehyde. The gas is generated in great amounts in a few seconds. The receptacle should be large enough to contain 10 times the volume of the Solution of Formaldehyde, as there is a tendency for the mixture to foam over the sides of the container.

Another practical method is to spray sheets with formaldehyde solution. The solution (37%) should be sprayed on sheets suspended in the room in such a manner that the solution remains in small drops on the sheet. Spray not less than 10 ounces of Solution of Formaldehyde for each 1000 cubic feet. Used in this way a sheet will hold about 5 ounces without dripping or the drops running together. The room must be sealed very tightly in disinfecting with this process and kept closed not less than twelve hours. The method is limited to rooms or apartments not exceeding 2000 cubic feet. The formalin may also be sprayed upon the walls, floors, and objects in the room.

Phenol.—It is soluble in water to the extent of about 5% and in such strength it is an efficient disinfectant. The solution should be made with hot water.

In standardizing disinfectants phenol is used as the standard. It is expensive, however, and there is often difficulty in making up satisfactory solutions. More efficient and more convenient is the *Liquor Cresolis Compositus, U.S.P.* This may be prepared by mixing equal parts of cresol and soft soap. This has a value according to tests made in the Hygienic Laboratory of 3, making it in tests without organic matter three times as efficient as phenol. Under similar conditions lysol had a value of 2.12, creolin 3.25 and trikresol of 2.62.

Equal parts of a 5% solution of Liq. Cresol. Co. and the faeces, urine or sputum to be disinfected is satisfactory for disinfection provided the mixture is allowed to stand for one hour. Here we would have the effect of a 2.5% solution. Liq. Cresol. Co. (5%) is an excellent disinfectant for contaminated bed clothing, etc. It is also most suitable for the disinfection of floors and walls.

Sulphate of Copper.—This salt in dilutions of 1:100,000 to 1:1,000,000, has a remarkable destructive effect on certain species of algae; upon snails and larvae of *Anopheles*.

Hydrogen Dioxide.—A 2% solution will kill anthrax spores in three hours. It is useful in treatment of anaerobic infections, as with the gas bacillus. When hydrogen dioxide is used in the presence of blood or pus, the catalase of the latter rapidly decomposes the H_2O_2 so that the disinfecting power rapidly disappears. The quality of hydrogen peroxide cannot be depended upon on account of its rapid deterioration.

Lime.—It must be remembered that air-slaked lime is inert as a disinfectant. For disinfecting faeces freshly prepared milk of lime is excellent. It is made by mixing unslaked lime with four times its volume of water. An equal quantity should be added to the faeces to be disinfected.

Chlorinated Lime.—This can be purchased in air-tight containers and when the package is opened it should give off a powerful odor of chlorine. Frequently samples fail to yield 30% of available chlorine (the U.S.P. requirement).

For a working disinfectant solution add 1 pound to 2 gallons of water, allow insoluble matter to settle and decant the clear liquid. This is satisfactory for mopping floors and for disinfecting faeces, sputum and urine, equal parts of the excreta and disinfecting solution being mixed and allowed to stand for one hour.

Chlorine.—The use of chlorine in the disinfection of drinking water has been considered above, see page 1729.

Eusol.—A solution containing 0.27% hypochlorous acid and known as eusol has been highly recommended in the treatment of gas gangrene wounds. To make it, put 12.5 grams chlorinated lime (bleaching powder) in a Winchester quart flask and cover with a liter of water. After thorough shaking add 12.5 grams of boric acid. After again shaking the mixture should stand for a few hours and then be filtered through cotton wool. The clear solution is *eusol*. It must be kept in tightly closed bottles.

Chloramine-T.—This chlorine antiseptic is more stable than hypochlorite solutions and can be used in greater concentration. It is non-toxic and readily soluble in water. It is usually used in 2% solution in the treatment of wounds. Gauze which has been impregnated with a 5% solution and dried can be used in light packing of wounds. In the eye, 0.1% (1–1000) in physiological saline is efficacious and non-irritating.

Dichloramine-T.—This, like chloramine-T, is a crystalline substance, but is practically insoluble in water. It is a very active germicide. In use it is dissolved in chlorinated eucalyptol or better still chlorinated paraffin wax (chlorcosane). For treatment of infected wounds it is used in 6.5 to 10% strength, the chlorinated oil solution of the antiseptic being sprayed on the wound or gauze covering the wound.

Acriflavine.—Of the dyestuffs recommended as germicides this is better adapted to the purpose than malachite green or brilliant green. Acriflavine, or flavine as it is also called, acts more efficiently in serum mixtures than in aqueous ones and is less injurious to tissue than most other antiseptics. It is generally used in 1–1000 solution in salt solution and makes a good wet dressing when gauze is soaked in such a solution.

Dakin's Solution.—The best known and most widely used of the disinfectants of the chlorine-group is a neutral sodium hypochlorite solution called Dakin's solution. This contains not more than 0.5% or less than 0.45% NaOCl in a neutral solution.

The usual method of preparing Dakin's solution is to make a 1.4% solution of anhydrous Na_2CO_3 and slowly introduce chlorine gas from a cylinder provided with a flow meter, adding 4.8 Gm. or 1600 cc. of gas per liter of solution. To titrate, remove 10 cc., add 25 cc. of water, 5 cc. of 10% KI solution and 2 cc. glacial acetic acid. Add from a burette N/10 sodium thiosulphate solution until brown color is discharged. Amount should be from 12.1 to 13.4 cc. If necessary, dilute with 1.4% Na_2CO_3 solution. Test reaction with phenolphthalein as described below.

The following method of preparing Dakin's solution was formerly used in the chemical laboratory of the Naval Medical School and is recommended if chlorine gas in cylinders is not available.

(A)	Bleaching powder	100 Gm.
	Water	1000 cc.
	Shake to mix thoroughly.	
(B)	Sodium carbonate	45 Gm.
	Sodium bicarbonate	48 Gm.
	Water	1000 cc.
	Dissolve completely.	

Mix A and B and shake vigorously for 5–10 minutes or allow to stand in a closed container a few hours. Then filter. This filtrate is the Dakin's solution which will be neutral to solid phenolphthalein (flash of red with alcoholic solution), but will contain about two to three times the amount of NaOCl required. Determine exact per cent of NaOCl and dilute to proper strength as follows:

Put 10 cc. of the filtered Dakin's solution in a 100-cc. volumetric flask. Add 20 cc. of 10% KI and 2 cc. of glacial acetic acid. Dilute to mark with H_2O and mix thoroughly. Put this wine-colored solution in a burette. In Erlenmeyer flask put 5 cc. of N/10 sodium thiosulphate (24.8 Gm. $Na_2S_2O_3.5H_2O$ per liter of H_2O) and add 2 cc. of starch paste for an indicator. (The starch paste is best made by mixing 1–2 Gm. of starch with about 10 cc. cold water and pouring this into 90 cc. of boiling water.) From

the burette run this solution into the 5 cc. of thiosulphate until a faint blue color results. This is the end-point. Take the reading on the burette and calculate the per cent NaOCl as follows:

Calculation:

$$\frac{18.615}{\text{cc. of solution from burette}} = \text{per cent NaOCl}$$

$$\frac{50}{\text{per cent NaOCl}} = \text{the number of cc. of above solution required to dilute to 100 cc. to make 0.5\% NaOCl.}$$

Example:

29 cc. of solution from the burette were required to reach the end-point.

$$\frac{18.615}{29} = 0.64\% \text{ NaOCl.}$$

$\frac{50}{0.64} = 77.88$ cc. So take 77.88 cc. of the Dakin's solution and dilute to 100 cc.

This will give 0.5% NaOCl, the required per cent.

Equations involved in the above are as follows:

$$CaCl(OCl) + Na_2CO_3 = NaOCl + NaCl + CaCO_3$$
$$NaOCl + HC_2H_3O_2 = HOCl + NaC_2H_3O_2$$
$$2KI + 2HC_2H_3O_2 = 2HI + 2KC_2H_3O_2$$
$$HOCl + 2HI = I_2 + HCl + H_2O$$
$$I_2 + 2Na_2S_2O_3.5H_2O = Na_2S_4O_6 + 2NaI + 10H_2O$$

Disinfestants

By disinfestants we mean those agents used for the destruction of rodents and insects.

Gaseous Disinfestants

Among the fumigants effective against both rodents and insects we have sulphur dioxide, hydrocyanic acid gas, Zyklon-B which was authorized for use in the Public Health Service in 1926, and cyanogen chloride gas. These are destructive to all forms of animal life. Hydrocyanic acid gas and cyanogen chloride gas do not injuriously affect merchandise, textiles, etc. and require less time for exposure than sulphur dioxide. Although sulphur dioxide has the manifest disadvantages of rotting fibres of textiles and bleaching certain dyed fabrics, its safety of application makes its use preferable to cyanide fumigants by those inexperienced in large scale fumigation. Prior to fumigation of vessels the crew should be mustered and all absentees accounted for in order that none might remain in the compartments to be fumigated. Thereafter measures should be taken to prevent the entry of any unauthorized person to such compartments until the medical officer has pronounced them safe for occupancy. In fumigating for rats a check is made after fumigation to insure that no rats remain alive. If necessary, fumigation is repeated. After fumigation, hatches, ventilators, doors, etc. are opened from the outside. The Public Health Service uses "Aerothrusts" (portable gasoline motors with airplane blade fans to remove the gas from holds and spaces having poor ventilation). They do not enter the superstructure for at least 15 minutes after opening up and do not enter the holds until they have been open an hour. In addition a tame rat in a cage is lowered to the bottom of the hold and left for at least five minutes to test for hydrocyanic acid gas or cyanogen chloride gas. If the rat is unaffected, the medical officer goes personally or observes one of his men go through all the compart-

ments before they are declared safe for occupancy. Men doing this carry an anti-cyanide gas mask in the alert position, are equipped with searchlights, and are watched from the deck.

Sulphur Dioxide.—For destruction of rats 5 pounds of roll or sublimed sulphur are burned per 1000 cubic feet of space. Shallow pans should be used for the sulphur which is sprinkled with alcohol and ignited. Precautions should be taken against fire by elevating the pans by means of bricks, etc., in a larger vessel containing water. Exposure for six hours is necessary. Two pounds of sulphur per 1000 cubic feet with two hours exposure are sufficient for destruction of mosquitoes, whereas for body lice four pounds per 1000 cubic feet with six hours exposure are required. Liquefied sulphur dioxide may be employed instead of burning sulphur, two pounds of the gas being substituted for each pound of sulphur. Machinery may be protected from the action of sulphur dioxide by coating the metal parts with lubricating grease. If clothing is washed immediately after sulphur fumigation the rotting effect will be lessened.

Hydrocyanic Acid Gas.—For destruction of rats 5 oz. sodium cyanide of high purity, 7½ oz. commercial sulphuric acid (66B) and 10 oz. water are required for each 1000 cubic feet of space. Exposure for two hours is necessary. The water is placed in a crock and the acid is run in cautiously immediately before fumigation in order to take advantage of the heat generated. The sodium cyanide, contained in a cloth bag, is dropped in the diluted acid by an operator who wears a special anti-cyanide gas mask. The ordinary military gas mask does not protect against hydrocyanic acid gas and cyanogen chloride. Sodium cyanide "eggs" of the proper weight are to be preferred to the loose cyanide. Liquid hydrocyanic acid in cylinders is efficient but dangerous to transport. For generation of HCN for destruction of insects Creel and Faget employed materials in the following proportions: potassium cyanide 1 part, commercial sulphuric acid (66B) 2 parts and water 2½ parts by weight. The following amounts of potassium cyanide per 1000 cubic feet of space were recommended: for *mosquitoes* 0.4 ounce, 15 minutes exposure; for *bed bugs* 5 ounces, exposure for one hour; for *body lice* 10 ounces, two hours exposure; for *roaches* 10 ounces, one hour exposure.

The Public Health Service now use Zyklon Discoids (a trade name of American Cyanamid & Chemical Corporation). These contain 5 per cent chlorpicrin (a lacrimator) with HCN absorbed in paper pulp, which is cut out in the form of thin discs. Two ounces HCN per 1000 cubic feet of space are used.

Cyanogen Chloride Gas.—This gas has been used as a substitute for hydrocyanic acid gas. Its lachrymatory and irritant properties even in non-lethal concentration are efficient to warn of its presence. It does not injure foodstuffs, textiles, etc. For fumigation against rats the Public Health Service has employed 4 oz. sodium cyanide, 0.8 to 1.6 oz. sodium chlorate (exact amount varies with conditions not yet determined), 17 oz. commercial hydrochloric acid, and 17 oz. of water per 1000 cubic feet of space. The acid and water are mixed in barrels, crocks or buckets and the sacks containing the dry chemicals are dropped into the mixture by men wearing anti-cyanide gas masks. "Eggs" containing a mixture of sodium cyanide and sodium chlorate may be purchased and will obviate the hazard connected with mixing the loose chemicals.

Pulicides.—For destruction of rat fleas one must accomplish the simultaneous destruction of rats by fumigation, bait poison, trapping, etc.

Among the liquid pulicides we have (1) crude petroleum (fuel oil) which is at times called Pesterine, (2) an emulsion of kerosene oil made as follows: Kerosene 20 parts, soft soap 1 part and water 5 parts. The soap is dissolved in the water by the aid of heat and the kerosene gradually stirred into the hot mixture.

As a *general insecticide* a mixture of 0.3 per cent pyrethrins (esters of the monovalent and divalent chrysanthemum acids) and 2.5 per cent B,B′ thiocyanodiethyl ether (5 per cent Lethane 384, a trade name of Rohm & Haas for 50 per cent by volume of the aliphatic thiocyanate) in deodorized kerosene is a very efficient liquid insecticide (spray). As a supplement to the spray, a mixture in an inert carrier (sulphur, talc or clay) of pyrethrum powder and powdered derris or cube in such proportions as to give a content of 0.4 per cent pyrethrins and 1 per cent rotenone yields a highly successful insecticide powder.

Carboxide gas (a trade name of Union Carbide and Carbon Chemicals Corporation), which contains 10 per cent ethylene oxide in carbon dioxide, has been found useful as an insecticide when employed in the concentration of 6 pounds per 1000 cubic feet of space. The period of fumigation required is 3 hours (for a sealed space). (See also p. 700.)

Pediculicides.—Owing to the great importance of lice in transmitting typhus fever, trench fever and relapsing fever their destruction is a vital consideration.

Although the body louse is the important transmitting agent, the head louse and possibly the crab louse should also be destroyed.

The subject of pediculosis has been much discussed on account of its importance among the troops in the World war.

For the destruction of head lice Pernet recommended:

1. Prevention: hair to be kept close cropped and clean.
2. For the nits: wipe them off with a solution of 1 in 30 phenol.
3. For the lice themselves: Unguentum hydrargyri ammoniati, diluted (gr.x to 1 oz.), or any fatty, sticky body well rubbed into the back of the head. Paraffin lamp-oil (kerosene) also good, but not to be used near an open flame or light.

Blanchard considers camphorated alcohol or warm vinegar containing 1 to 1000 corrosive sublimate as useful for head lice. He also suggests the fumigation of clothes with tobacco as valuable for body lice.

For the destruction of body lice Pernet recommends:

1. All body and bed-linen and clothes should be baked or sterilized by boiling.
2. Unguentum staphisagriae should be applied to neck-bands of vests and shirt in the region of the neck.
3. Alkaline baths to soothe the irritated skin.

Sublimed sulphur or naphthaline sprinkled in the bed and the clothes is very useful.

Castellani and Jackson have gone most extensively into the matter of louse destruction. Their conclusions are as follows: 1. In regard to solid and liquid insecticides, the substances which have been found to be deleterious to body lice are in the order of their efficiency: Kerosene oil, vaseline, guaiacol, anise preparations, iodoform, lysol, cyllin and similar preparations, phenol solution, naphthalene, camphor.

Pyrethrum has a very feeble action on lice, and boric acid, sulphur, corrosive sublimate, and zinc sulphate, when used in powder form, have apparently no action whatever. As regards bedbugs, kerosene oil is the best insecticide. Next to it comes guaiacol, one of the most active drugs of those tried.

For ridding the body of lice the following steps are essential

1. The hair of the body and head should be clipped.
2. The subject should be bathed, there being used freely kerosene-emulsion soap, prepared by boiling 1 part of soap in 4 parts of water, and then adding 2 parts of kerosene oil. The resultant jelly, when mixed with 4 parts of water, makes a liquid soap that is convenient to use and which may be applied effectively.
3. Following the bath, the body may be anointed with kerosene, special care being devoted to the hairy parts. Skin irritation may, however, require early removal of the oil.
4. It has been found that lice on clothing removed from the body may remain alive nine days and their eggs as long as forty days. The clothing, therefore, should be disinfested by one of the following methods.

(*a*) Steam; (*b*) boiling for five minutes; (*c*) 5% compound cresol solution for 30 minutes; (*d*) fumigants such as sulphur dioxide and hydrocyanic acid gas. Chlorpicrin has also been employed.

5. In the absence of facilities for carrying out the steps described, or to prevent infestation subsequently, dusting powders are sometimes used. Of these the N.C.I. powder, containing commercial naphthalene, 96 Gm., creosote, 2 cc., and iodoform, 2 Gm., is the most widely known; but Moore's powder—creosote, 1 cc.; sulphur, 0.5 Gm., and talc, 20 Gm.—is less irritating and is said to be six times as effective. It has also been recommended to wring out the underclothes in 5% compound cresol solution and then dry thoroughly, or to impregnate them with substances such as the halogenated phenols.

Raticides.—For large scale extermination of rats, especially during an outbreak of plague, fumigation with sulphur dioxide, hydrocyanic acid gas or cyanogen chloride gas is the most efficient method. For exterminating rats and in this way secondarily the rat fleas, besides the ordinary poisons such as As, P, etc., Rucker has recommended a poison composed of plaster of Paris 6 parts, pulverized sugar 1 part and flour 2 parts. This mixture should be exposed in dry place in open dishes. To attract the rats the edge of the dish may be smeared with the oil in which sardines have been packed. Phosphorus is the base of many of the commercial rat poisons. Its inflammable nature is a drawback. Furthermore rats soon learn to recognize its odor and refuse to eat food containing this poison. Barium carbonate is highly regarded as a rat poison, having neither taste nor odor. It is mixed with meal and bacon fat—about 1 part of barium carbonate to 4 parts of meal. In trapping rats one should frequently change the type of trap, and always allow the traps to be placed about the storehouse without being set for a day or so, to accustom the rat to its harmlessness. Again they should be handled with gloves so that they may not carry the odor of man. In the use of spring traps every effort should be made to disguise them by covering with saw dust, straw, chaff or meal. Bacterial vaccines, as the Danysz virus, are not considered satisfactory and are dangerous as possible causes of food poisoning in man.

Larvicides.—When drainage and filling of mosquito-breeding areas are not practicable and the use of fish not possible, various larvicidal agents may be used. The most common of these are petroleum, both crude and refined, Panama larvicide, (p. 1734) crude phenol, cresol and a mixture of soft soap and petroleum. Trioxymethylene (paraformaldehyde) has been mentioned by Roubaud and others as being efficient against anopheline larvae. The Marine Barracks at Quantico, Va., reported satisfactory results from the use of oiled sawdust in 1918. Barber and Hayne published an account of the use of Paris green mixed with inert dust to form a surface-deposit in 1921. The observation that Paris green is effective against the surface feeding anophelines but has no effect on culicine larvae has been confirmed by subsequent observers. One pound per acre is efficient, and in open water without vegetation much smaller quantities suffice. Airplanes equipped with hoppers lend themselves to thorough and economical distribution of larvicides. The Department of Agriculture tried dusting with Paris green from airplanes manned by Army pilots in 1923. Since that time airplanes have been used in various parts of the country to distribute Paris green and oiled sawdust. Oiled sawdust is probably the best general larvicide for use in this manner. Dry fine sawdust is impregnated with a mixture made from equal volumes of crank case oil and kerosene. It takes four to ten days to effect saturation depending upon the kind of sawdust used. Excess oil is permitted to drain from the impregnated sawdust before it is used.*

Destruction of Mosquitoes.—Measures of protection against the immediate danger of infection from the adult mosquito merit attention. Screening, fumigation, repellents and swatting constitute the usual means.

Carter stated that wire screening with 16 meshes to the linear inch will exclude anophelines. Number 18 screen (18 meshes to the inch) was adopted in the Isthmus to exclude *Aëdes aegypti* which may pass through number 16 screen. It is manifest that screening will not be effective unless particular attention is given to stopping up cracks around the doors, window screens and elsewhere. Holes through which pipes pass, drains, fireplaces not in use and even key holes should pe sealed against mosquitoes. Canvas strips were found by von Ezdorf to be convenient in making window screens and screen doors tight. In quarters for temporary occupancy fine cloth netting nailed outside the windows and secured with battens will do. In infected areas where screening is not possible mosquito bars, 20 mesh bobbinet, should be used on beds but must be properly applied to afford protection. They should be suspended so that they hang some distance over the mattress and inside the head and foot pieces of the bed so that the edges may be tucked in snugly under the mattress when one goes to bed. Howard states tlat the wearing of veils and gloves after sundown enforced at stations on the Italian railroads some years ago resulted in a great reduction of malaria.

* Russell (1940) has used successfully water instead of dust for dilution.

The fumigants usually employed to destroy mosquitoes are dry sulphur dioxide, pyrethrum and Mim's culicide (phenol-camphor). The U. S. Public Health Service has also used hydrocyanic acid gas for this purpose.

Dry sulphur dioxide produced by burning 2 pounds of sulphur for every 1000 cubic feet is very effective if the spaces are made tight by stuffing or sealing all cracks and openings. Two hours exposure is sufficient. The vessels in which the sulphur is to be burned should rest on bricks or in a tub of sand to prevent fire but should not rest in water as is done in ordinary fumigation. It is said that in the absence of moisture sulphur dioxide causes no injury to household goods, fabrics or metals.

Pyrethrum is used in the proportion of 2 pounds to 1000 cubic feet. The powder is ignited, and after two hours exposure the mosquitoes must be swept up carefully and burned as pyrethrum, although it stuns the mosquitoes, cannot be depended on to kill. The expense is another deterrent to its use.

Mim's culicide is made by triturating equal parts of camphor and phenol. The resulting liquid is volatilized by gentle heat, 4 ounces being used for each 1000 cubic feet. Goldberger states that, like pyrethrum, the fumes of this culicide stun but do not necessarily kill the mosquitoes. Care should be taken not to overheat this substance as the vapor is likely to catch fire. The lamp used to heat the container should stand in a vessel of water for this reason. In the absence of a convenient support, a piece of stovepipe is cut to form three legs. An alcohol lamp is inserted to heat a flat basin resting on the other end of the pipe.

Creel and Faget found that exposure for 15 minutes to the gas from 0.4 ounce of potassium cyanide per 1000 cubic feet of space was sufficient to kill mosquitoes. The amount for 1000 cubic feet yields "approximately 1 part cyanogen to 6000 parts of air, so dilute, in fact, as to practically eliminate all danger to human life. On repeated occasions we entered the fumigating room immediately upon opening the doors after mosquito fumigation without noticing any ill effects." In generating the hydrocyanic acid gas they used potassium cyanide, c.p., sulphuric acid (66B) and water combined in the proportions by weight of 1 part cyanide, 2 parts acid, and 2½ parts water.

For houses that cannot be screened properly by reason of their construction, Coogle found commercial creosote oil to be practical as a repellent for anopheline mosquitoes. The ceilings and walls of 25 houses in various sections of an anopheline-infested area were sprayed in the proportion of 1 gallon of creosote oil to 420 square feet. Anopheline mosquitoes were found in all the houses on several visits prior to the treatment. After spraying, no anopheline mosquitoes were found in any of these houses during three inspections at three-weeks intervals. Apparently the occupants did not object to the creosote oil and no ill effects were noted in any of those who slept in the rooms subsequent to the spraying.

Volatile oils, particularly citronella, pennyroyal, lavender and cedar, are commonly used on exposed parts of the body as repellents. Spirit of camphor, kerosene, oil of peppermint, oil of tar, lemon juice and vinegar have also been recommended. Samotz recommends dilution with 4 parts of liquid petrolatum to retard the evaporation of oil of citronella. Repellents to be applied to the body are poor substitutes for screening when we have to do with infective mosquitoes.

Communicable Disease Control on Aircraft

Following the action of an International Convention for Aerial Navigation, at the Hague, in 1933, regulations concerning measures to prevent the introduction of communicable diseases have been established. As regards passengers, these follow the lines adopted for other modes of transportation. The communicable diseases which are the subject of special measures are: plague, cholera, yellow fever, exanthematous typhus, and small pox. In these regulations the period of incubation is reckoned as follows: 6 days for plague; 5 days for cholera; 6 days for yellow fever; 12 days for typhus; and 14 days for small pox. Re-ratization and disinsectization measures are prescribed when indicated.

Mosquito Destruction.—Aircraft from tropical countries are required to take steps to destroy mosquitoes before arrival at a United States port. This is accomplished by

spraying a culicide inside the aircraft compartments, which must not be toxic to human beings. Furthermore, it must be noninflammable.

The essentials of the spray formerly advocated were one part of pyrethrum extract in oil and four parts of a light oil or carbon tetrachloride. The pyrethrum extract is such that one gallon of the extract contains the pyrethrins extracted from 20 pounds of standard pyrethrum flowers, the latter containing at least 0.9% of pyrethrins as determined by chemical assay. The light oil is one approximating the characteristics of kerosene, and may vary within considerable limits provided the flash point is not too low.

The mixture may be made up in any proportions of extract, oil and carbon tetrachloride, providing only that the extract is at least 20%. For example, it may be any of the following: 1 part of extract with 4 parts of oil; 1 part extract, 3 parts oil and 1 part carbon tetrachloride; 1 part extract, 2 parts oil and 2 parts carbon tetrachloride; 1 part extract, 1 part of oil and 3 of carbon tetrachloride; and 1 part extract and 4 parts carbon tetrachloride. The last named was the mixture that had been specifically advocated by the Public Health Service, because it is to all intents and purposes completely noninflammable. Some objection has been raised to its use, however, because the carbon tetrachloride is slightly toxic. Whether it is to be used or not is not of particular moment from a quarantine standpoint, being a point which must be settled in accordance with the fire hazard.

Any of these mixtures when sprayed through the air in the form of very fine droplets in the amount of 5 cc. per thousand cubic feet of space will fatally poison mosquitoes within 5 to 10 minutes.

The action of the pyrethrins on mosquitoes, and probably on other insects, is due apparently to direct absorption following actual wetting of the surface by the pyrethrins in solution. It is for this reason that it is essential that at least 20% of the mixture be an oil that does not immediately evaporate. If 100% carbon tetrachloride is used with the same pyrethrin content, the lethal effect is much less, presumably due to the rapid evaporation of the carbon tetrachloride and the consequent precipitation of the pyrethrins in solid form.

There has been objection made to the use of carbon tetrachloride by some of the aviation executives. Furthermore, it was suggested that a combination of pyrethrin and rotenone might be more efficient and more culicidal than pyrethrin alone. Rotenone is a white crystalline compound obtained from derris and other plant sources. These questions have recently been studied by Asst. Surgeon General C. L. Williams of the United States Public Health Service and a concentrated, noninflammable pyrethrum spray is now recommended which has been shown to be highly toxic to mosquitoes while practically innocuous to human beings. In order to prevent especially the introduction into the United States of yellow fever, through mosquitoes carried by aircraft from South American and other foreign parts; to prevent the introduction of *Anopheles gambiae* from eastern South America into the southern part of the United States; and to prevent the introduction of any *Anopheles* from the west coast of the United States into the Hawaiian Islands, the present United States Public Health regulations require that "The operating officials and pilots of aircraft from South American ports shall be instructed that, during flight, after taking off from the last foreign port and before arriving at the first American port, and also after leaving any United States insular port and before arriving at any United States continental port, each aircraft shall be adequately sprayed, in all accessible compartments, with a pyrethrum spray which shall contain not less than four-tenths per cent pyrethrins and not less than twenty per cent of kerosene, or a similar oil, in amounts of not less than five cubic centimeters for every thousand cubic feet of space, and that, during such spraying, all openings into the aircraft shall be closed and held closed for a period of not less than five minutes after spraying is completed. In the event that any aircraft fails to carry out adequate disinsectization as here prescribed, such disinsectization shall be carried out by employees of the quarantine station before any persons on said aircraft are permitted to disembark." In Reprint No. 2169, *U. S. Public Health Reports*, Vol. 53, No. 23, 1940, Williams describes in detail "Disinsectization of Aircraft" and also the construction of

a new insecticide sprayer which obviates difficulties previously experienced and renders the process simple and effective. Freon pyrethrum aerosol issued by the quartermaster, U.S.A. has proved most effective. Insect repellent No. 612 (2-ethyl hexanediol 1,3) manufactured by the National Carbon Company has proved to be an excellent repellent for flying and crawling insects. Indalone is a somewhat less efficient repellent. Dimethyl phthalate is excellent and perhaps better against some species than 612. DDT (Dichlor-diphenyl trichlorethane), Gesarol or Neocid, said to have been discovered by the Geigy Company in Switzerland, is probably the most superior of all insecticides. It has, however, no action upon ticks and no lethal effect on human itch mites.

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Composition of Ordinary Food Materials
(From Lusk, after Atwater and Bryant)

Kind of food material	Inedible refuse of purchased material, %	Edible portion: Water, %	Un-available nutrients, %	Available nutrients: Protein, %	Fat, %	Carbohydrates, %	Ash, %	Fuel value per lb. = 453.6 grams, calories
Beef (fresh):								
Ribs	20.8	55.5	2.0	17.0	25.3	....	0.7	1430
Round, lean	8.1	70.0	1.0	20.7	7.5	....	1.1	735
Hind quarter	15.7	59.8	1.8	17.8	20.5	....	0.7	1240
Beef (preserved and cooked):								
Canned, corned	....	51.8	2.7	25.5	17.8	....	3.0	1275
Roast, cooked	....	48.2	2.4	21.6	27.2	....	1.0	1410
Veal (fresh):								
Hind quarter	20.7	70.9	1.2	20.1	7.9	....	0.8	740
Liver	....	73.0	0.9	9.7	5.0	....	1.0	410
Lamb (cooked):								
Chops, broiled	13.5	47.6	2.5	20.1	28.4	....	1.4	1640
Leg, roast	....	50.9	2.1	24.3	21.5	....	0.9	1410
Pork (pickled, salted and smoked):								
Ham	13.6	40.3	3.6	15.8	36.9	....	3.6	1905
Pork (cooked):								
Ribs, cooked	....	33.6	3.1	24.1	35.7	....	1.7	2020
Poultry and game (fresh):								
Fowl	25.9	63.7	1.6	18.7	15.5	....	0.8	1040
Fish (fresh):								
Cod steaks	9.2	79.7	0.9	18.1	0.5	....	0.9	385
Mackerel	44.7	73.4	1.3	18.1	6.7	....	0.9	650
Shell-fish (fresh):								
Oysters, in shell	81.4	86.9	0.8	6.0	1.1	3.7	1.5	235
Fish (preserved and canned):								
Cod, salt, boneless	1.6	55.0	5.5	24.9	0.3	...	14.3	510
Salmon, canned	14.2	63.5	1.9	21.1	11.5	....	2.0	915
Eggs:								
Eggs, boiled	11.2	73.2	1.2	12.8	11.4	....	0.6	755
Dairy products, etc:								
Whole milk	....	87.0	0.5	3.2	3.8	5.0	0.5	310
Skimmed milk	....	90.5	0.3	3.3	0.3	5.1	0.5	170
Cheese	....	34.2	3.4	25.1	32.0	2.4	2.9	1885
Butter	....	11.0	4.9	1.0	80.8	....	2.3	3410
Miscellaneous:								
Gelatin	....	13.6	3.2	88.7	0.1	....	1.6	2125
Cereals, etc.:								
Corn (maize) meal	....	12.5	4.0	7.5	1.7	73.5	0.8	1625
Oatmeal, boiled	....	84.5	0.9	2.3	0.5	11.3	0.5	285
Rice, boiled	....	72.5	1.1	2.3	0.1	23.8	0.2	505
Gluten flour	....	12.0	4.6	11.0	1.6	70.1	0.7	1630

COMPOSITION OF ORDINARY FOOD MATERIALS.—(*Continued*)

Kind of food material	Inedible refuse of purchased material, %	Edible portion: water, %	Un-avail-able nutri-ents, %	Available nutrients: Pro-tein, %	Fat, %	Carbo-hydrates, %	Ash, %	Fuel value per lb. = 453.6 grams, calories
Wheat flour:								
Family and straight grade	....	12.8	4.0	8.3	1.0	73.5	0.4	1615
Bread								
Corn (johnnycake)	....	38.9	3.5	6.5	4.2	45.2	1.7	1170
White wheat	....	35.3	3.3	7.1	1.2	52.3	0.8	1195
Sugar, starches, etc:								
Sugar, granulated	....	....	...	....	....	100.0	...	1790
Vegetables:								
Asparagus, fresh	....	94.0	0.7	1.3	0.2	3.3	0.5	95
Beans, lima, green	55.0	68.5	2.7	5.3	0.6	21.6	1.3	525
Beans, stringed, cooked*	....	95.3	0.5	0.6	1.0	1.9	0.7	90
Beans, baked	....	68.9	2.8	4.8	2.3	19.6	1.6	565
Beets, cooked	....	88.6	1.2	1.7	0.1	7.2	1.2	170
Cabbage	15.0	91.5	0.7	1.2	0.3	5.5	0.8	140
Carrots, fresh	20.0	88.2	1.0	0.7	0.4	8.9	0.8	200
Sweet corn, green	61.0	75.4	1.8	2.3	1.0	19.0	0.5	445
Lettuce	15.0	94.7	0.5	0.9	0.3	2.9	0.7	85
Peas, green, cooked*	....	73.8	2.5	5.1	3.1	14.4	1.1	490
Potatoes, cooked, boiled	....	75.5	1.7	1.9	0.1	20.0	0.8	415
Spinach, cooked*	....	89.8	1.1	1.6	3.7	2.7	1.1	235
Sweet potatoes, cooked*	....	51.9	3.0	2.2	1.9	40.3	0.7	885
Turnips	30.0	89.6	0.8	1.0	0.2	7.8	0.6	175
Vegetables (canned):								
Beans, string	....	93.7	0.7	0.8	0.1	3.7	1.0	90
Sweet corn	....	76.1	1.7	2.1	1.1	18.3	0.7	430
Peas, green	....	85.3	1.4	2.7	0.2	9.6	0.8	235
Tomatoes	....	94.0	0.5	0.9	0.2	3.9	0.5	100
Fruits, etc. (fresh):								
Apples	25.0	84.6	1.6	0.3	0.5	12.8	0.2	260
Bananas	35.0	75.3	2.7	1.0	0.5	19.9	0.6	400
Blackberries	....	86.3	1.5	1.0	0.9	9.9	0.4	235
Grapes	25.0	77.4	2.4	1.1	1.4	17.3	0.4	390
Oranges	27.0	86.9	1.4	0.6	0.2	10.5	0.4	210
Pears	10.0	84.4	1.7	0.5	0.4	12.7	0.3	255
Fruits, etc. (dried):								
Dates	10.0	15.4	8.8	1.6	2.5	70.7	1.0	1415
Figs	....	18.8	8.7	3.4	0.3	67.0	1.8	1290
Raisins	10.0	14.6	9.1	2.0	3.0	68.7	2.6	1410
Prunes	15.0	22.3	8.3	1.6	....	66.1	1.7	1230
Fruits, etc. (canned):								
Peaches	....	88.1	1.3	0.5	0.1	9.8	0.2	190
Pears	....	81.1	1.9	0.3	0.3	16.2	0.2	310
Nuts:								
Almonds	45.0	4.8	10.9	17.8	49.4	15.6	1.5	2685
Cocoanuts	49.0	14.1	9.2	4.8	45.5	25.1	1.3	2460
Peanuts	25.0	9.2	10.7	21.9	34.7	22.0	1.5	2255

* *With butter, etc., added.*